

**MINISTRY OF HIGHER AND SECONDARY SPECIALIZED
EDUCATION OF THE REPUBLIC OF UZBEKISTAN
HEALTHCARE MINISTRY OF THE REPUBLIC OF UZBEKISTAN**

TASHKENT PHARMACEUTICAL INSTITUTE

In the rights of handwritten

UDC 615.453.62

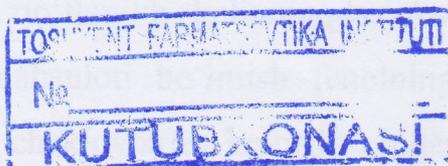
SHAMSHIDDINOVA MAFTUNA KHUSNIDIN QIZI

**The composition and technology of tablets made on the base of complex
of pyridoxine hydrochloride and nicotinamide with nickel**

5A 510603 – Industrial technology of drugs

Dissertation for getting the academic degree of Master

Scientific tutor: ass.prof., phd. Khaydarov V.R.



TASHKENT – 2016

MINISTRY OF PUBLIC HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY

**TOPICAL ISSUES
OF NEW DRUGS DEVELOPMENT**

Vol. 1

April 21, 2016
Kharkiv

Kharkiv
NUPh
2016

CONTENT

SYNTHESIS OF PHYSIOLOGICALLY ACTIVE SUBSTANCES	5
Albaan Mustafa S., Berezniakova N. L.	6
Albany Ali, Ieromina Z. G., Grinevich L. O., Sych I. A., Perekhoda L. O.	7
Andriyev O. O., Bosnjak E. M., Kolisnyk O. V., Moskalenko I. M.	8
Artemenko A. A., Redkin R. G., Schemchuk L. A., Chernykh V. P.	10
Artemenko A. A., Volkogon A. O. Redkin R. G., Schemchuk L. A., Chernykh V. P.	12
Artemov D., Radul O., Dragalin I., Barba A., Uncu L., Valica, Macaev F.	13
Artemyuk O. P., Berkalo Y. A., Bylov I. E., Brizitskaya O. A.	15
Artemyabaka Meriame, Abu Sharkh A. I., Bezugly P. O.	16
Artemyugina V., Skorobohatova V., Golik M. Yu.	17
Artemyulina Y. G., Arzumanov P. S., Shemchuk L. A.	18
Artemyut S., Duca Gh., Valica V., Macaev F.	19
Artemyhenko T. I., Lega D. A., Shemchuk L. A., Chernykh V. P.	21
Artemyruha K. O., Tsapko Ye. O.	22
Artemyova Ya. V., Brizitskaya O. A., Bylov I. E.	23
Artemyov G. V., Shemchuk L. A., Chernykh V. P.	24
Artemyvska O. S., Berezniakova N. L., Kiz O. V.	25
Artemyadov T., Yaremenko V. D.	26
Artemyic A. V.	27
Artemyov S., Podolsky I. M.	29
Artemyana V. R., Kovalenko S. S., Kovalenko S. M., Zaremba O. V., Artemy D. V., Bondarenko A. B., Langer T.	30
Artemyana N. V., Chan T. M.	32
Artemyhaiberdiyev A., Podolsky I. M.	34
Artemynal Y. O., Perekhoda L. O., Sych I. A., Ieromina Z. G.	35
ArtemyJamil, Sych I. A., Grinevich L. O., Ieromina Z. G., Perekhoda L. O.	36
Artemyana A. A., Sytnik K. M., Kolisnyk S. V.	37
Artemyenko O. D., Krolenko K. Yu., Vlasov S. V., Zhuravel I. O., Artemy Chernykh V. P.	39
Artemyry Y. Y., Tsapko T. O., Zubkov V. O.	41
ArtemyGotmy, Drapak I. V., Sych I. V., Tsapko T. O., Perekhoda L. O.	42
Artemyeva D. A., Berezniakova N. L.	44
Artemyshiddinova M. Kh., Saydaliyeva A. K., Khaydarov V. R.	45
Artemyrova D. V., Snehrov V. P., Bevz N. Y., Almakaeva L. G.	47
Artemyenko I. V., Shpychak T. V., Shemchuk L. A.	48
ArtemyYa. I., Gorizdra I. A., Shpychak T. V., Chernykh V. P.	49

THE SYNTHESIS PROCESS AND THE STUDY OF COMPLEX MATTER OF NICKEL WITH PYRIDOXINE AND AMID OF NICOTINIC ACID

Shamshiddinova M. Kh., Saydaliyeva A. K., Khaydarov V. R.

Tashkent Pharmaceutical Institute, Tashkent, Uzbekistan

shamshiddinovamaftuna@gmail.com

Introduction. All cells and tissues of the human body contain the chemical elements in the free state and as a set of chemical compounds. Medical properties of elements and their compounds, usually close or identical. These compounds include complexes and components characteristic to a living organism. With the development of the chemistry, scientists began to note that the action of, for example, metals may be enhanced with the formation of compounds with medicinal substances that are specific to one or another disease. This is because in the body the chemical elements are mainly in the form of coordination compounds that usually have a high biological activity, therapeutic efficacy and safety.

Aim. The main goal of the research is to synthesize the complex matter of nickel with pyridoxine and amid of nicotinic acid, as well as studying its properties.

Materials and methods. The synthesis process of the complex is divided into two stages. Pyridoxine is usually manufactured in the form hydrochloric salt. The first stage is receiving the base of pyridoxine from its hydrochloric salt. 20.00 g of pyridoxine hydrochloride and 8.12 g of sodium bicarbonate are ground in a mortar to the fine powder. Pyridoxine hydrochloride is dissolved with 250 ml of ethanol. Consequently, the sodium bicarbonate is added partly into the previous solution and continuously stirred by heating (70-75 °C) until the carbon dioxide removed completely. After that, the solution of pyridoxine is separated from the precipitate of sodium chloride. The precipitate is washed with small amount of ethanol and added to the pyridoxine solution. Solution of pyridoxine is evaporated 1/5 of the original volume and precipitated with 200 ml of ether. The precipitate is filtered, then washed with ether and dried. The next stage is related to the synthesis of complex of nickel with pyridoxine and the amide of nicotinic acid. 0.06 mole of pyridoxine and 0.02 mole of amide of nicotinic acid were resolved in 200 ml of ethanol. 0.02 mole of ethanolic solution of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ is combined with a solution of bioactive ligands and stirred on a magnetic stirrer during the 5 hours. The precipitated mass is filtered, then washed with ethanol and ether. The obtained complex is provisionally called by the name of "Pymicam". The structure of complex was studied by the method of IR-spectroscopy, while the thermal property was determined with TGDSC analysis.

Results and discussion. The synthesized powder of complex is green colored, tasteless and with characteristic odor. In the IR-spectrum of the complex was obtained by the IR-spectroscope of Shimadzu (Japan) in the Republican drug



ЎЗБЕКИСТОН РЕСПУБЛИКАСИ ФАНЛАР АКАДЕМИЯСИ
АКАДЕМИК О.С. СОДИКОВ НОМИДАГИ
БИООРГАНИК КИМЕ ИНСТИТУТИ



ТАЪЛИМ, ФАН ВА МАДАНИЯТ
МАСАЛАЛАРИ БЎЙИЧА
БИРЛАШГАН МИЛЛАТЛАР ТАШКИЛОТИ

СЕРТИФИКАТ

CERTIFICATE

This is to certify that:

Maftuna Shamsiddinova

*“Талаба ва ёш тадқиқотчилар учун кристаллография бўйича
малака ошириш машғулотлари” амалий курсини муваффақиятли тамомлади
has successfully completed "Training courses for capacity building of students and
young scientists in the field of crystallography"*



A.S. Turayev
Институт директори проф. Тураев А.С.
Director of the Institute prof. A.S. Turayev

Илмий марказ бошлиғи проф. Ибрагимов Б. Т
Head of research center prof. B. T. Ibragimov

O'ZBEKISTON RESPUBLIKASI
OLIV VA O'RTA MAXSUS TA'LIM VAZIRLIGI
O'ZBEKISTON RESPUBLIKASI
SOG'LIQNI SAQLASH VAZIRLIGI
TOSHKENT FARMATSEVTIKA INSTITUTI

Fakultet - Sanoat farmatsiyasi

Ilmiy rahbar: dots.,f.f.n. Xaydarov

Kafedra-Dori vositalarining

V.R.

sanoat texnologiyasi

Mutaxassisligi: 5A 510603-

O'quv yili 2014-2016 y.

Dorilarning sanoat texnologiyasi

Magistratura talabasi:

Shamshiddinova M.X.

MAGISTRLIK DISSERTATSIYASINING ANNOTATSIYASI

Mavzuning dolzarbligi. So'nggi yillarda qandli diabet kasalligi rivojlangan mamlakatlarda dolzarb tibbiy muammoga aylanib bormoqda. Ushbu kasallik bilan og'riyotgan bemorlar orasida chaqaloqlar va yosh bolalarning mavjud ekanligi achinarli xoldir. Insonlar o'limiga sababchi bo'layotgan kasalliklar qatorida qandli diabet kasalligi yurak ishemik kasalligi va onkologik kasalliklardan so'ng uchinchi o'rinni egallaydi. Butunjahon Sog'liqni Saqlash tashkilotining bergan ma'lumotiga ko'ra ushbu kasallikka chalinganlarning soni 2015-yilga kelib 300 million kishiga yetgan bo'lsa, 2035-yilga kelib 398 mln ga yetishi kutilmoqda. Bizning mamlakatimizda ham qandli diabet bilan kasallanganlar soni kundan-kunga ortib bormoqda va endokrin kasalliklari ichida 4-o'rinni egallagan. 1950-yillar oxirida taklif etilgan sulfanilmochevina va benzamid preparatlari va ularning analoglari bugungi kunda ham asosiy davolovchi vosita sifatida qo'llanilib kelinmoqda. Ammo ularning nojo'ya ta'sirlari va metabolizm mahsuloti bo'lmish fenolning toksik ta'siri ushbu dorilarni qo'llashda turli cheklovlarni keltirib chiqarmoqda. Davlatimiz tomonidan aholini sifatli, bezarar va yuqori biosamaradorlikka ega dori

vositalari bilan ta'minlash ishlariga alohida e'tibor berib kelinmoqda. O'zbekiston Respublikasining "Fuqarolar sog'lig'ini saqlash to'g'risida" gi (1996-yil 29-avgust) va "Dori vositalari va farmatsevtika faoliyati to'g'risida" gi (1997-yil 25-aprel) qonunlarida mamlakatda dori vositalari muomalasining qonuniy asoslari yaratilgan. Yuqoridagilarga asosan respublikamizda qandli diabet bilan kasallangan bemorlar davlatimiz tomonidan kerakli dori-darmonlar bilan ta'minlanib kelinmoqda. Biroq bu dorilar xorij mamlakatlaridan import asosida keltirilganligi uchun ular dorixonalarda yuqori narxda sotilmoqda. Shuning uchun hozirda mahalliy xom ashyolar asosida tibbiyot amaliyoti uchun yuqori samaraga ega bo'lgan qandli diabetga qarshi ta'sir ko'rsatadigan dori vositalarini yaratish amaliy ahamiyatga egadir.

Ishning maqsadi va vazifalari. Toshkent farmatsevtika instituti "Anorganik, analitik, fizik va kolloid kimyo" kafedrasida xodimlari tomonidan sintez qilib olingan va qandli diabet kasalligiga qarshi faol ta'sir ko'rsatadigan "Pirnikam" kompleks birikmasidan tabletka ishlab chiqarish uchun maqbul tarkib va texnologiyani tanlash asosiy maqsad qilib belgilandi. Maqsadga erishish uchun quyidagi vazifalarni hal qilishga to'g'ri keldi:

- sintez qilib olingan "Pirnikam" (nikelning piridoksin va nikotinamidli kompleks birikmasi) substansiyasining fizik, kimyoviy, farmakologik va mikrobiologik xossalarini o'rganish;
- substansiyadan tabletka dori turini olish uchun uning texnologik xossalarini o'rganish, yordamchi moddalarni tanlash va maqbul texnologik jarayonni ishlab chiqish;
- olingan tabletkalarni standartlash;
- tabletkalarning biologik samaradorligini in vitro usulida o'rganish;
- tabletka dori turining saqlanish muddatini belgilash;

Tadqiqot obyekti va predmeti. Tadqiqotning obyekti "Pirnikam" substansiyasi bo'lib, ushbu substansiya asosida yaratilgan tabletka tadqiqotning predmetidir.

Tadqiqot uslubiyati va uslublari: Tadqiqot jarayonida zamonaviy fizik-kimyoviy tahlil usullari (IQ-spektroskopiya, UB-spektroskopiya, optik-spektral mikroskopiya, TGDSK, YuSSX), texnologik va biofarmatsevtik usullar, klinikagacha bo‘lgan farmakologik izlanishlar qo‘llanilgan.

Tadqiqot natijalarining ilmiy jihatdan yangilik darajasi. Ilk bor kompleks birikma asosida qandli diabetga samarali ta’sir ko‘rsatuvchi tabletka dori turi tarkibi va texnologiyasi ishlab chiqildi, tabletkalarning sifat ko‘rsatkichlari baholandi.

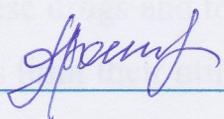
Tadqiqot natijalarining ilmiy amaliy ahamiyati va tatbiqi. O‘rganilgan “Pirnikam” substansiyasi asosida yaratilgan tabletka dori turini gipoglikemik vosita sifatida respublikamiz farmatsevtik korxonalarida ishlab chiqarishga tatbiq etish mumkin.

Ishning tuzilishi va tarkibi. Dissertatsiya kirish, asosiy qism, xulosa, ilovalar va adabiyotlar ro‘yxatidan iborat. Ish 74 betdan iborat bo‘lib kompyuterda yozilgan. Ish o‘z tarkibiga 18 jadval va 16 ta grafikni olgan.

Bajarilgan ishning asosiy natijalari. “Pirnikam” substansiyasining fizik-kimyoviy, farmakologik, mikrobiologik va texnologik ko‘rsatkichlari aniqlandi, substansiyadan tabletka dori turini olish uchun yordamchi moddalar tanlandi va maqbul texnologiya ishlab chiqildi. Tabletkaning sifat ko‘rsatkichlari baholandi, biosamaradorligi in vitro usulida o‘rganildi va saqlanish muddati aniqlandi.

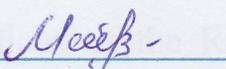
Xulosa va takliflarning qisqacha umumlashtirilgan ifodasi. Olingan natijalar “Pirnikam” substansiyasidan olingan tabletkalarni tibbiyot amaliyotiga tadbiq etish uchun asos bo‘ladi.

Ilmiy rahbar


(imzo)

dots.,f.f.n. Xaydarov V.R.

Magistratura talabasi


(imzo)

Shamshiddinova M.X.

**MINISTRY OF HIGHER AND SECONDARY EDUCATION OF
THE REPUBLIC OF UZBEKISTAN**

MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

TASHKENT PHARMACEUTICAL INSTITUTE

Faculty: Industrial Pharmacy

Supervisor: Ass/Prof, Phd.

Major: Industrial technology of drug

Khaydarov V.R.

facilities

Speciality: 5A 510603 Industrial

The academic year 2014-2016

technology of drugs

Master student:

Shamshiddinova M.Kh.

ABSTRACT

Actuality of the work. Recent years, diabetes is becoming a major medical problem all over the world, especially in developed countries. Unfortunately, the list of diseased people with diabetes includes children and even infants. According to the disease category that causes death the diabetes takes the third rank after cancer and heart ischemic diseases. According to data of the World Health Organization in 2015, the number sick people captured with diabetes has grown to 300 million people, consequently it is predicted that this number is exceeded up to 398 million in 2035. Also in our country, the number of diabetic patients is augmenting progressively and this illness takes the fourth leading position among the endocrine diseases. Since 1950 preparations of sulfonylurea, biguanide and their derivatives have been using as the primary medicine for diabetes. But the side effects of these drugs and toxicity of phenol which occurs after the metabolism of these drugs limit their utilization. Our government gives special attention in supplying the population with high-quality, safe and highly effective medicines. The regulations of the Republic of Uzbekistan “About healthcare of citizens” (1996, 29th of august) and “About drug facilities and pharmaceutical activity” (1997, April 25th) created the legal basis of the drug usage and production in the state level. On the base of the above mentioned

diabetic patients are provided with the necessary medicines by government. In spite of this, these drugs are imported and sold in pharmacies on the high prices. Therefore, at the moment discovery on the high efficiency antidiabetic medication made on the basis of local raw materials and their implementation into the medical practice have practical significance.

The purpose and tasks of research. The main goal of research is to choose the optimal composition and technology for the tablet manufacturing based on substance "Pyrnicam" which is synthesized by the employees of the department of "Inorganic, analytical, physical and colloid chemistry" of the Tashkent Pharmaceutical Institute. To achieve the goal we have solved the following tasks:

- To study the physical, chemical, pharmacological and microbiological properties of the synthesized substance "Pyrnicam";
- Explore the technological properties of the substance, choose the appropriate excipients and develop an optimal technology for the preparation of tablets;
- Standardization of tablets;
- Study of the biological activity by vitro method;
- The study of the shelf life of the tablets.

The object and the subject of research. The object of the research is "Pyrnicam" substance and the subject of study is a tablet derived from initial active substance.

The research techniques and methods. During the research the modern physico-chemical methods (IR spectroscopy, UV spectroscopy, optic-spectral microscopy, TGDSC, HPLC), technological and biopharmaceutical and preclinical methods were used.

The degree of novelty of scientific research results. For the first time the composition and technology of tablets of complex compound which is active in diabetes was developed and evaluated the qualitative properties of tablets.

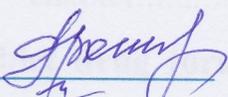
The scientific and practical significance of the study results. The tablets contain the substance of "Pyrnicam" can be implemented for manufacturing at pharmaceutical companies as a hypoglycemic drug.12

The structure and the composition of work. The thesis consists of introduction, four main body chapters, conclusions and applications. The work is presented on 74 pages of computer text, including 16 graphs 18 tables and a bibliography list includes 64 names.28

The main results of research. The physical, chemical, pharmacological, microbiological and technological properties of "Pyrnicam" substance were studied, excipients were selected and optimal technology for producing tablets was developed. The qualitative properties of tablets were identified as well as biological activity of drug is studied by in vitro method and durability of tablets was researched by "Accelerated aging" method.32

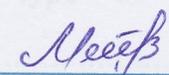
Short generalized expression of the conclusions and proposals. These results deserve to the implementation of tablets which are obtained from the substance of "Pirnikam" into medical practice.39

Supervisor


(signature)

Ass/Prof, Phd. Khaydarov V.R.

Master student


(signature)

Shamshiddinova M.Kh.

Contents

Introduction.....	9
Chapter I. Literature review.....	12
1. The analysis of world pharmaceutical market.....	12
2. The pharmaceutical sector of Uzbekistan.....	17
3. The legal bases of pharmaceutical manufacturing.....	25
4. Determination of tablets as dosage form.....	28
5. Drugs which is made from complex substances.....	30
6. Conclusion for the 1 st chapter.....	32
Chapter II. Physicochemical, technological, pharmacological and microbiological properties of complex of nickel with pyridoxine and nicotinamide.....	34
1. Physicochemical properties of the complex of nickel with pyridoxine and amide of nicotinic acid.....	34
2. Technological properties of the substance nickel complex with pyridoxine and nicotinic acid amide.....	39
3. Certain pharmacological and microbiological properties of complex matter.....	44
4. Conclusion for the 2 nd chapter.....	48
Chapter III. Obtaining tablet drug form from complex matter of nickel with pyridoxine and amid of nicotinic acid.....	50
1. The amount and type of the auxiliary substances for tablet preparing.....	50
2. The technology of tablet drug form from researched substance.....	54
3. Standardization process of tablets.....	63
4. Conclusion for the 3 rd chapter.....	74
Chapter IV. Studying the biological effectiveness and shelf life of tablets.....	75
1. Research of biological efficacy of tablets with the method of in vitro.....	75

2. Studying the shelf life of tablets with the method of accelerated ageing.....	77
3. Conclusion for the 4 th chapter.....	80
Concluding clauses.....	81
Bibliography cited.....	84
Appendix.....	90

people captured with diabetes has grown to 300 million people, consequently it is predicted that this number is exceeded up to 398 million in 2035. Also in our country, the number of diabetic patients is augmenting progressively and this disease takes the fourth leading position among the endocrine diseases. Since 1950 preparations of sulfonylurea, biguanide and their derivatives have been using as the primary medicine for diabetes. But the side effects of these drugs and toxicity of phenol which occurs after the metabolism of these drugs limit their utilization. Our government gives special attention in supplying the population with high-quality safe and highly effective medicines. The regulations of the Republic of Uzbekistan "About healthcare of citizens" (1996, 20th of august) and "About drug facilities and pharmaceutical activity" (1997, April 15th) created the legal basis of the drug usage and production in the state level. On the base of the above mentioned diabetic patients are provided with the necessary medicines by government. In spite of this, these drugs are imported and sold in pharmacies on the high prices. Therefore, at the moment discovery of the high efficiency antidiabetic medication made on the basis of local raw materials and their implementation into the medical practice have practical significance.

Object and subject of research. The object of the research is "Pymicinam" substance and the subject of study is a tablet derived from initial active substance.

The aim and tasks of research. The main target of research is to choose the optimal composition and technology for the tablet manufacturing based

INTRODUCTION

Validity and topicality of dissertation theme. Recent years, diabetes is becoming a major medical problem all over the world, especially in developed countries. Unfortunately, the list of diseased people with diabetes includes children and even infants. According to the disease category that causes death the diabetes takes the third rank after cancer and heart ischemic diseases. According to data of the World Health Organization in 2015, the number sick people captured with diabetes has grown to 300 million people, consequently it is predicted that this number is exceeded up to 398 million in 2035. Also in our country, the number of diabetic patients is augmenting progressively and this illness takes the fourth leading position among the endocrine diseases. Since 1950 preparations of sulfonylurea, biguanide and their derivatives have been using as the primary medicine for diabetes. But the side effects of these drugs and toxicity of phenol which occurs after the metabolism of these drugs limit their utilization. Our government gives special attention in supplying the population with high-quality, safe and highly effective medicines. The regulations of the Republic of Uzbekistan “About healthcare of citizens” (1996, 29th of august) and “About drug facilities and pharmaceutical activity” (1997, April 25th) created the legal basis of the drug usage and production in the state level. On the base of the above mentioned diabetic patients are provided with the necessary medicines by government. In spite of this, these drugs are imported and sold in pharmacies on the high prices. Therefore, at the moment discovery on the highefficiency antidiabetic medication made on the basis of local raw materials and their implementation into the medical practice have practical significance.

Object and subject of research. The object of the research is “Pyrnicam” substance and the subject of study is a tablet derived from initial active substance.

The aim and tasks of research. The main target of research is to choose the optimal composition and technology for the tablet manufacturing based on

substance "Pyrnicam" which is synthesized by the employees of the department of "Inorganic, analytical, physical and colloid chemistry" of the Tashkent Pharmaceutical Institute. To achieve the goal we have solved the following tasks:

- To study the physical, chemical, pharmacological and microbiological properties of the synthesized substance "Pyrnicam";
- Explore the technological properties of the substance, choose the appropriate excipients and develop an optimal technology for the preparation of tablets;
- Standardization of tablets;
- Study of the biological activity by vitro method;
- The study of the shelf life of the tablets.

Scientific novelty. For the first time the composition and technology of tablets of complex compound which is active in diabetes was developed and evaluated the qualitative properties of tablets.

The main problems and hypothesis of research. Research on new composition on tablet drug form contains complex matter of nickel and their standardization methods. The main techniques are taken from British Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia.

Literature review of dissertation theme. Conception of world pharmaceutical market, pharmaceutical manufacturing in Uzbekistan; pharmaceutical law and regulations, especially Presidential decrees and resolutions; tablet drug forms, the advantages and disadvantages of usage of tablets; complex matters and drugs made on the base of complex substances; physic-chemical, biopharmaceutical, technological research on drug manufacturing; the results of the analysis of the types and prospects for their development; local pharmaceutical manufacturing capacity; drug development and evaluation of the drug quality; the determination of pharmacological effects of drug; the stability and durability of tablets.

Description of methodology used in research. During the research the modern physico-chemical methods (IR spectroscopy, UV spectroscopy, optical microscopy, TGDSC, HPLC), technological (size and shape of particles, the fractional content, friability, powder density, compression, moisture content etc.) and biopharmaceutical and preclinical methods were used.

Practical and theoretical importance of research results. The tablets contain the substance of "Pyrnicam" can be implemented for manufacturing at pharmaceutical companies as a hypoglycemic drug.

The structure of work. The thesis consists of introduction, four main body chapters, conclusions and applications. The work is presented on 74 pages of computer text, including 16 graphs 18 tables and a bibliography list includes 64 names.

I CHAPTER. LITERATURE REVIEW

1. The analysis of world pharmaceutical market.

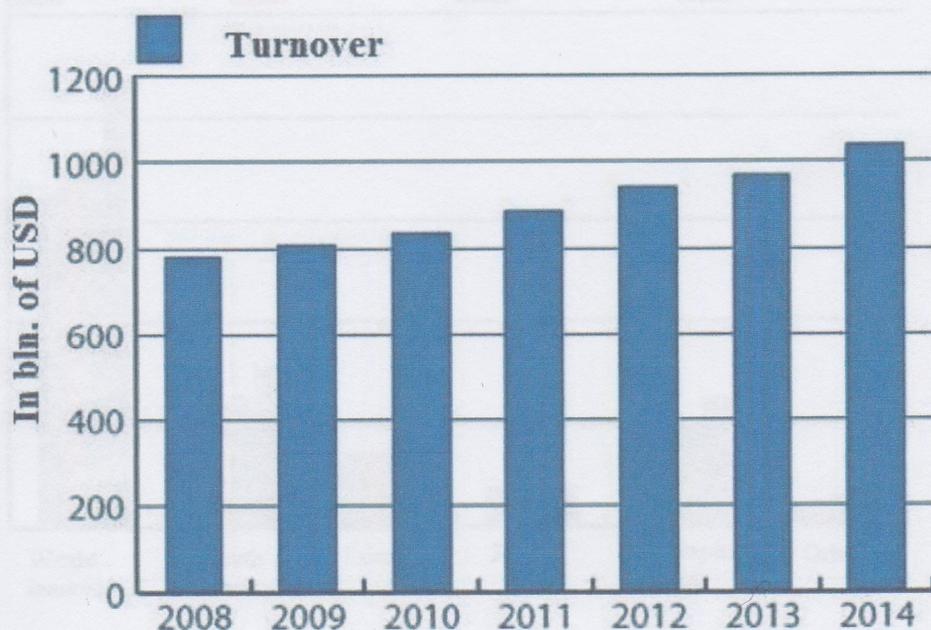
At the end of XX century the world pharmaceutical market (WPM) was served as a field of activity for powerful manufacturers and scientists to create and develop the medical items and drugs for consumers. The uniqueness of the WPM that contains the processes of the improvement of health needs of population, health preservation and prophylaxis can be took it into the vital and necessary category of life. This feature makes a significant influence on the demand formation, which depends on the production, supply, product range, market conjuncture and capacity etc [33].

The historical evidences show that the primitive pharmaceutical market was revealed in the early socio-economic structure of human beings, whereas the drugs of plant, animal or mineral origin were exchanged on some material goods rather than money. Currently, the pharmaceutical industry is one of the most difficult and wide areas of the chemical industry, that consists of a huge number of sub-sectors.

Today, the pharmaceutical industry takes a great importance for the health of all inhabitants of our planet. As one of the important sectors of the global economy, the pharmaceutical industry has a significant impact in neighboring areas: health care, insurance business, finance, petrochemicals, biotechnology, as well as military-industrial complex. The stable rates of production and profit growth is characterized the strength of pharmaceutical industry, according to analysts, the growth of the demand for drugs in the world virtually independent from the ups and downs of the economy. For example, in countries such as Japan, USA, France, Switzerland, Belgium, Germany, the annual drug consumption per capita numbered to \$ 250. In a large group of countries like Sweden, Canada, Finland, Denmark, the Netherlands, Italy, UK, Spain, Portugal, Argentina, Greece, Ireland it varies in the range of 100-250 dollars. In Czech Republic, Hungary, Poland, Russia, Bulgaria the expenditure of medicines does not exceed \$ 50-100 [57].

According to the «IMS Health Consulting» International research company estimates, the global pharmaceutical market reached \$ 1.039 billion in 2014, which is 7% more than in 2013 (Fig.1).

Fig. 1. The dynamics of the global pharmaceutical market in 2008-2014, in bln. of USD.



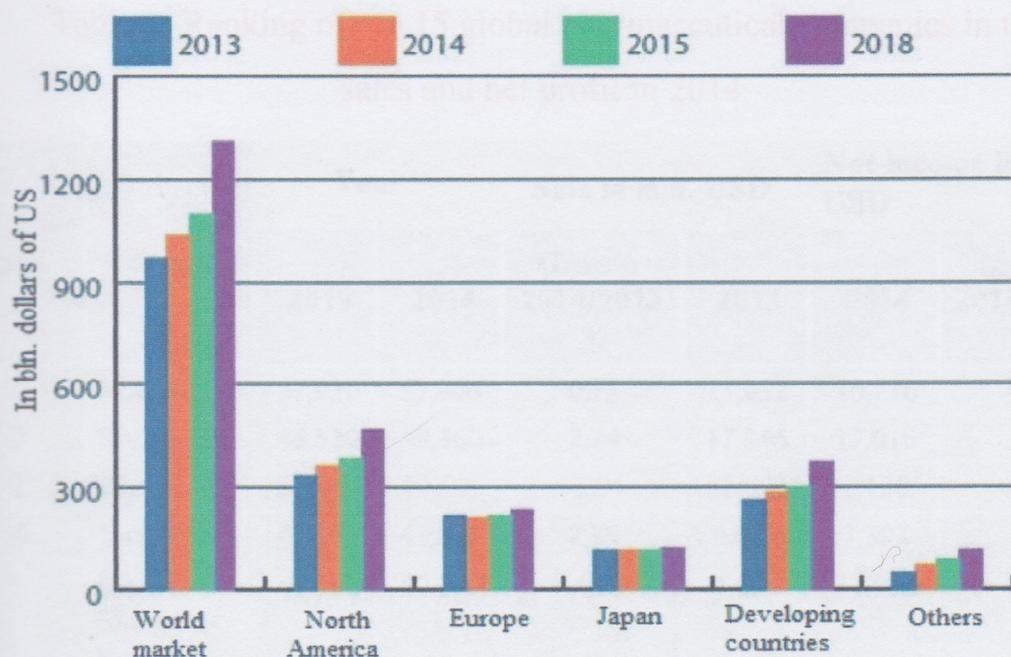
Source: IMS Health, 2014

21 countries belonging to the group of “Pharmerging Markets” were the engine of the market growth, increasing the share from 24% in 2013 to 28% in 2014. The most dynamic pharmaceutical market of this group was the Chinese market, which grew by 13.5% in 2014. This was promoted by a significant improvement in the infrastructure of health care system and the increment in the number of private hospitals that increased the population access to medicines. It is planned, that the Chinese pharmaceutical market growth will slow down a bit and stop at the level of 10-12% till 2018, and reach \$ 170 billion in 2018.

The «Pharmerging Markets» determined the dynamics of growth in Latin America and developed countries according to generics and unbranded medications, as well as the developed countries showed the growth due to innovative medicines. According to analysts, the annual growth will not be less

than 4-7%, therefore it is expected that the volume of the global pharmaceutical market will exceed \$ 1.3 trillion in 2018 (Fig.2).

Fig. 2. The development of the global pharmaceutical market and changes in the territorial distribution of its volumes in 2012-2018, in bln. of USD



Source: IMS Health, 2014

In 2014, the greatest number of new molecules was registered. 41 new drugs were approved by US FDA in the last year, which was the highest figure since the last century and outbid the data by 41% in 2013. At the same time the status of a fundamentally new drug was given to the 9 drugs.

The focus of research is on those therapeutic groups that have the greatest market potential and have the great growth opportunities (eg. oncology, diabetes, tuberculosis). In 2014, 4 new molecules have been recorded and the market volume of the segment numbered to \$ 81 billion, consequently the annual growth increase by and reached \$ 153 billion in 2020, while the global market of prescription drugs will increase by only 5-6% [54].

Analysis of the results of economic activities of the leading pharmaceutical companies demonstrates that the future - for manufacturers who are investing heavily funds in the development of innovative, in particular biotechnological

Drugs and do not spare money for the purchase of innovative companies (Tab.

D) ... manufacturing subsidiary Sanofi.

This kind of pharmaceutical manufacturers always intend to be at the list of top pharmaceutical companies.

Table 1. Ranking of top 15 global pharmaceutical companies in terms of sales and net profit in 2014

Rate	Company	Year		Sale in mln. USD		Net-income in mln. USD	
		2013	2014	Growth 2014/2013, %	2013	2014	Growth 2014/2013, %
1	Novartis	57,920	57,996	0,13	11,952	10,736	-10
2	Roche	48,530	49,860	2,74	17,346	17,016	-2
3	Pfizer	51,584	49,605	-3,84	22,003	9,135	-58
4	Sanofi	42,080	43,070	2,35	6,687	7,393	11
5	Merck-SharpDohme	44,033	42,237	-4,08	4,404	11,920	171
6	Glaxo-SmithKline	41,613	37,960	-8,78	10,640	10,883	2
7	Johnson & Johnson	28,125	32,300	14,9	6,882	7,433	8
8	Astra-Zeneca	25,711	26,095	1,49	8,865	10,216	15
9	Bayer	24,170	25,470	5,38	6,552	6,997	7
10	Gilead Sciences	10,800	24,890	130,46	3,100	12,100	290
11	Teva	20,314	20,272	-0,21	1,649	3,951	140
12	Amgen	18,676	20,063	7,43	5,867	6,191	6
13	Abbvie	18,790	19,960	6,23	5,664	3,411	-40
14	Elli Lilly	23,113	19,616	-15,13	4,685	2,390	-49
15	BristolMyersSquibb	16,385	15,879	-3,09	2,580	2,004	-22

Source: annual report of pharmaceutical companies, 2014

Let us analyze more indicators of individual leaders. The Swiss company Novartis is the second year the head of global pharmaceutical market. Despite the fact that the company also suffered from the collapse of the patent (lost more than \$ 1 billion), it was able to show the increase in sales. This was achieved

because of the growth in sales of oncological and ophthalmic drugs, also the sale of generic manufacturing subsidiary Sandoz.

The Swiss concern Roche increased its sales in pulmonology and oncology segments in 2014. Sale of drugs such as Herceptin, Perjeta and Kadcylla grew by 20%.

The American company Pfizer continues losing its position in the ranking for the third consecutive year. It still couldn't compensate the decline in sales of blockbusters (Lipitor, Viagra, Celebrex), which ended the period of patent protection.

The French company Sanofi difficultly shows the growth indexes for several years. The sale drugs Lantus, Plavix and Lovenox makes a significant portion of the company's sales. The new basal insulin Toujeo intended to compensate partially for the growing competition in the biosimilar generic "Lantus".

The company Merck & Co. purchased the Schering Plough and entered the elite of the world pharma in 2009. This step has allowed to increase turnover and to achieve \$ 27.4 billion in 2011. However, stagnation was the main cause of decrease, numbered to 4% in 2014.

Regarding the British company GlaxoSmithKline the year was not the most successful for sales, it fell by almost 9%. AstraZeneca also faced with the problem of the patent expiration on the drug Nexium and Crestor.

The pharmaceutical direction Bayer Healthcare is increasingly becoming the key for the German company Bayer. According to the voiced plans, Bayer plans to sell its Material Science business unit and focuses on the pharmaceutical and agricultural business.

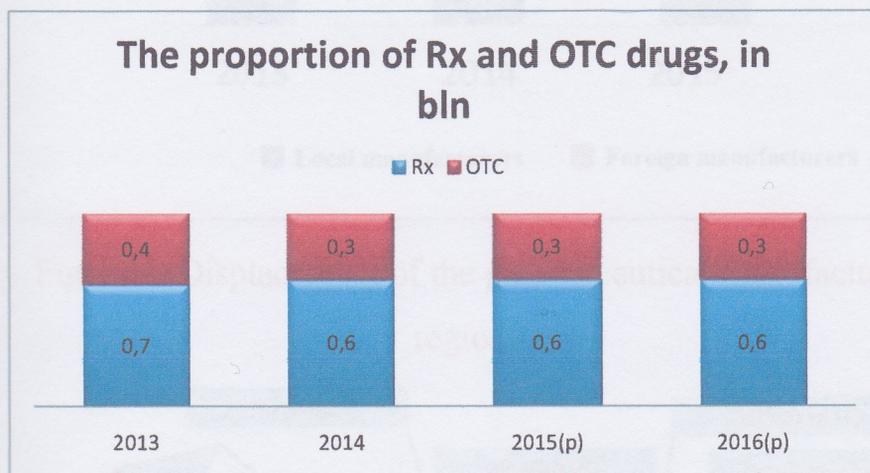
All companies are making efforts to softening the impact of external factors and protect their share in the WPM. The figures show that only companies with an emphasis on investing in innovation and searching the new treatment and prevention methods will be able to retain and even strengthen its position in the market.

2. The pharmaceutical sector of Uzbekistan

The pharmaceutical market is a strategic significant segment of any developed country's economy, as well as a security base of the fields like public health, drug and medical-technical ensuring. The pharmaceutical industry growth promotes a sustainable development of the social economy, consequently the improvement of people's life quality. In addition, the modern pharmaceutical industry – is a high-technological and science-intensive branch, which is linked with chemical manufacturing, agriculture and engineering in technological aspects and also other sectors of the economy [55].

Moreover, Uzbek pharmacy has already become the main backbone of republican economy and takes the second rank in relation to the national income.

Figure 3. The portion of prescribed and over the counter drugs in Uzbekistan's pharmaceutical market, in billions of US dollars



SOURCE Drugs' retail trade monitoring in Uzbekistan; Hospital purchases monitoring in Uzbekistan

Today, the number of pharmaceutical enterprises producing the generic and original drugs is reached to approximately 150. In accordance with Uzfarmsanoat company data, 7214 descriptions of goods are registered in the country, 1446 of which are domestic (Fig.3).

According to the VI-ORTIS company data in 2013 the pharmaceutical market of Uzbekistan numbered 1.11 billion US dollars, whereas the market volume decreased to 0.91 billion US dollars in 2014. Meanwhile, the market capacity was roughly 0.92 billion USD with +1.5% increment in 2015 and it is predicted that it would be equaled to 0.92 billion USD with +4% growth in 2016.

Figure 4 illustrates that only 25% of all currently registered drugs are domestic

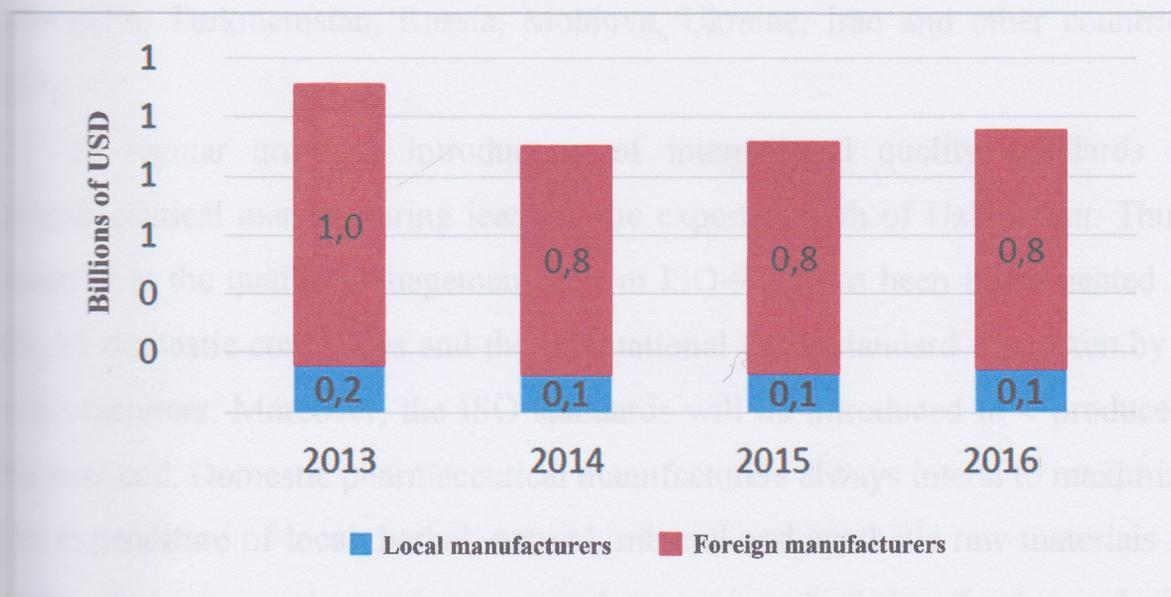
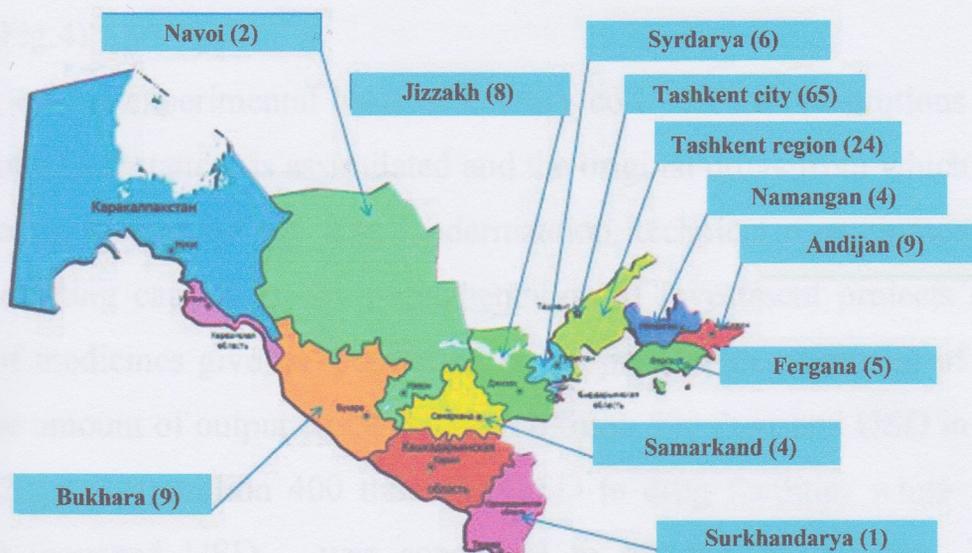


Figure 5. Displacement of the pharmaceutical manufacturers by regions



The numbers in the brackets are the amount of pharmaceutical companies

The export of outputs, made by the pharmaceutical enterprises of Uzbekistan was more than 21 00000 USD in the 1st half of 2013. According to NIA “Turkistan press” it is planned that export should reach to 3 800000 USD or increase to more than 78% by year end.

Today, more than 250 domestic drugs are registered in the 12 foreign countries by the enterprises of “Uzpharmsanoat” State joint-stock company (SJSC). As per “The Public word” issue the export of pharmaceutical products is settled up in Armenia, Azerbaijan, Afghanistan, Georgia, Kazakhstan, Mongolia, Turkmenistan, Russia, Moldova, Ukraine, Iraq and other countries [53].

A regular arranged introduction of international quality standards to pharmaceutical manufacturing leads to the export growth of Uzbekistan. Thus, recently at the quality management system ISO-9001 has been implemented in the 21 domestic companies and the international GMP standard was taken by 3 manufacturers. Moreover, the ISO standards will be introduced to 4 producers by year end. Domestic pharmaceutical manufacturers always intend to maximize the expenditure of local, herbal, natural, mineral and synthetic raw materials in elaboration of new drug substances and ready drug facilities. To this end, the cooperation of pharmaceutical producers with the Academy of Sciences, the Health Ministry of Uzbekistan and “Uzkimyosanoat” SJSC is being steadily developed (Fig.4).

Today, on the experimental basis of country core research institutions the production of 35 substances is assimilated and the original drugs from which are manufactured in the enterprises. The modernization, technical re-equipment of enterprises existing capacities, the implementation of investment projects and new types of medicines give the possibility to the positive development of the industry. The amount of output equaled to 298 million 800 thousand USD in the 1st half of 2013, 121 million 400 thousand USD to drug facilities while 135 million 700 thousand USD – was concerned to the medical devices. The production of auxiliary materials has reached 40 million 700 USD [56].

There are more than 160 pharmaceutical manufacturing factories and companies in Uzbekistan. Among them, a lot of enterprises established with foreign partners from Switzerland, Germany, Russia, China, Great Britain and other countries. During the years of independence the investments with more than 150 million USD was attracted in pharmaceutical industry, 90 million USD of which constituted foreign investments. Consequently, the drug production volume has increased from 46 million 900 thousand sums to 310 billion 210 million sums. As a result of this phenomena 1 thousand 265 drugs related to the 90 pharmacotherapeutic groups and 30 drug forms have been registered.

State policy and strategy for the development of pharmaceutical industry of the Republic of Uzbekistan is directed to encourage the production capacity growth, as well as to attract a foreign investment by providing privileges and preferences.

In particular, pursuant to the Presidential Decree PD-4434 from 10.04.2012 "On additional measures of encouragement to involve direct foreign investments" of the enterprise economy sectors, including the field of drugs, that involve direct private foreign investments are exempted from the tax payments due to the income and property, in addition single tax payment for the social infrastructure improvement and development, as well as for micro and small enterprises, compulsory contributions of Republican itinerary fund during the 3-7 years, depending on the volume of the investments [63].

Moreover, foreign investors that carry out their business in Uzbekistan, including the pharmaceutical manufacturing field are exempted from customs duties on the imported equipment and raw materials and materials for the production of medicines and medical items.

At the same time, national legislation provides huge privileges for domestic pharmaceutical manufacturers in participating in the international tenders for purchasing medicines on government purchase orders. Hence, the establishment of co-production companies creates an effective condition for the rapid development of the Uzbek drug market.

Over the last year a pharmaceutical sector has drawn roughly 76.53 million USD investments and 34.83 million USD direct overseas ones. The Uzbek pharmaceutical market volume reached to 1 billion USD and 80% of them were imported drugs. At the same time the average annual growth of market capacity equals to 25-30%. The market is dominated by the imported products mainly from Germany, France, India, USA, Russia and other countries [55].

Nowadays, there are 138 appropriate licensed ventures engaged in production of drug facilities and medical items in Uzbekistan. According to the drug productivity, "Jurabek Laboratories", "Nika Pharm" and "Nobel pharmsanoat" took the first three ranks among the other Uzbek pharmaceutical companies in 2013. The manufacturing capacity of pharmaceutical enterprises numbered to 420.5 billion sums (growth rate – 120.3 %) in 2013. Meanwhile, the amount of drug products reached 318.2 billion sums (growth rate – 109.5%), medical items - 58.1 billion sums (growth rate - 124,7%), auxiliary materials - 37.3 billion sums (growth rate - 496.0%) and other products - by 6.9 billion sums (growth rate - 103,6%). In real terms, output reached 688 million USD (growth rate - 134.7%).

The Uzbek pharmaceutical market structure review shows that the 30% of medicaments are produced in the tablet form and 28% in the form of solutions in vials and ampoules, and 17% in the state of dried powders. Currently, the main products of pharmaceutical companies are injection, infusion solutions, tablets, capsules, ointments, medical items, pharmaceutical vessels and others.

According to the State register of drug facilities of the Republic of Uzbekistan 6599 items of medicines and medical items were presented in the market by the 1st of January in 2013, whereas only 20% of them are produced in the home market. Also, leaders of the last 2 years in the development and introduction of new products are "Novopharma Plus", "Nika Pharm", "DentaFill Plus", "Nobel Pharmsanoat" and "Remedy Group", and it should be noted that 22 members of the "Uzfarmsanoat" SJS have the international quality certificate of ISO: "Novopharma Plus", "Nika Pharm", "Radiks", "Jurabek Laboratories",

“DentaFillPlus”, “Zamona Rano” , “NASA”, “Remedy”, “Remedy group”, “Uzgermed Pharm”, “Samsun-Tashkent-Pharm”, “Gufik-Avicenna”, “Asia Trade”, “Reka-Med Farm”, “SAMO”, “Elastikum”, “MerryMed Farm”, “Nobel Pharmsanoat”, “Galenika”, “Makrofarm-Optima”, “Immunomed” and “Pharmed”.

The geography of the Uzbek pharmaceutical export includes countries such as Afghanistan, Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Russia, Turkmenistan, Ukraine, Moldova, Mongolia and others. The export size numbered to 5,935,000 US dollars at the end of 2013.

Uzbek medicament manufacturers successfully cooperate with leading pharmaceutical companies of Germany, Russia, Turkey, India, China, South Korea, Poland, Bulgaria, the Czech Republic, Ukraine, Hungary and other countries. The investment involvement of republican pharmaceutical sector is assured by adequate market sale, simplified mechanism for the export of products, as well as the opportunity to enter the markets of neighbourhood countries (Fig.5).

Despite of the high pace of growth, a further evolvement is necessary for the national pharmaceutical industry. In the meantime, one of the priority tasks concerns the development of drugs based on native elaboration and local raw materials.

It is evident that Uzbekistan is rich in flora, including 138 families, 1023 generation and 4500 species of plants, including about 1,150 curative plants, therefore this prospect enables to produce the original drugs and dietary additives on the base of local raw materials and to ensure population with qualitative and affordable drugs.

In accordance with the Presidential Decree of the Republic of Uzbekistan from 24.07.2008 № PD-927 “On measures to improve the involvement process and disbursement of foreign investments and loans” 14 investment projects are developed and asserted in 2014 with the aim of manufacturing of medicines and

SOURCE: Ministry and export of drugs and medical devices in Uzbekistan

medical items. The total investment for implementation numbered to 155.7 million US dollars in respective year.

Table 2. Import of ready drug facilities in Uzbekistan between 2013 and 2014

Country	2014		2013		Import share in 2014, in natural terms	Import share in 2014, in money terms	Increment, %	
	Amount, in tonne	Value in 000 USD	Amount, in tonne	Value in 000 USD			Increment of amount, %	Increment in money, %
India	49 131	125 791	52 405	148 673	12%	16%	▼ -6%	▼ -15%
Germany	26 715	87 359	29 767	109 560	7%	11%	▼ -10%	▼ -20%
Russia	119 394	83 381	133 123	97 658	30%	11%	▼ -10%	▼ -15%
Ukraine	36 816	69 415	43 100	105 339	9%	9%	▼ -15%	▼ -34%
China	45 767	38 646	39 045	36 364	11%	5%	▲ 17%	▲ 6%
Byelorussia	42 193	34 115	42 087	28 732	10%	4%	○ 0%	▲ 19%
Slovenia	9 468	32 873	10 903	48 693	2%	4%	▼ -13%	▼ -32%
France	4 826	32 131	4 854	37 537	1%	4%	▼ -1%	▼ -14%
USA	2 500	29 651	4 059	46 244	1%	4%	▼ -38%	▼ -36%
Hungary	5 960	24 614	4 486	23 863	1%	3%	▲ 33%	▲ 3%
Austria	2 849	20 335	2 870	30 604	1%	3%	▼ -1%	▼ -34%
Spain	1 463	17 144	1 745	23 973	0%	2%	▼ -16%	▼ -28%
Georgia	5 861	16 695	6 667	21 062	1%	2%	▼ -12%	▼ -21%
Egypt	2 539	16 125	1 952	15 837	1%	2%	▲ 30%	▲ 2%
Pakistan	8 069	13 588	9 331	19 008	2%	2%	▼ -14%	▼ -29%
Poland	5 392	12 730	4 882	14 760	1%	2%	▲ 10%	▼ -14%
Italy	1 294	11 310	1 346	14 444	0%	1%	▼ -4%	▼ -22%
Turkey	2 696	11 309	2 973	14 680	1%	1%	▼ -9%	▼ -23%
Czech Republic	2 495	9 681	2 952	12 157	1%	1%	▼ -15%	▼ -20%
Denmark	844	9 624	1 976	21 158	0%	1%	▼ -57%	▼ -55%
Greece	934	7 844	759	8 196	0%	1%	▲ 23%	▼ -4%
Bulgaria	4 605	7 767	4 076	8 422	1%	1%	▲ 13%	▼ -8%
Iran	1 986	6 972	1 734	5 926	0%	1%	▲ 15%	▲ 18%
Romania	1 159	6 630	719	5 325	0%	1%	▲ 61%	▲ 25%
the Netherlands	656	6 273	696	8 044	0%	1%	▼ -6%	▼ -22%
Belgium	549	4 977	454	4 908	0%	1%	▲ 21%	▲ 1%
Latvia	838	3 854	679	3 692	0%	0%	▲ 23%	▲ 4%
Slovakia	610	3 523	719	4 596	0%	0%	▼ -15%	▼ -23%
Great Britain	522	3 113	487	3 418	0%	0%	▲ 7%	▼ -9%
Kazakhstan	5 853	3 049	3 677	1 665	1%	0%	▲ 59%	▲ 83%
SAR	394	3 034	271	2 603	0%	0%	▲ 46%	▲ 17%
Switzerland	204	2 978	223	3 137	0%	0%	▼ -9%	▼ -5%
Armenia	3 057	2 751	3 929	2 896	1%	0%	▼ -22%	▼ -5%
Korea	258	2 361	123	2 322	0%	0%	▲ 109%	▲ 2%
Moldova	1 615	2 202	1 689	2 620	0%	0%	▼ -4%	▼ -16%
Ireland	121	2 189	131	2 240	0%	0%	▼ -7%	▼ -2%
Croatia	278	2 126	233	3 080	0%	0%	▲ 19%	▼ -31%
Singapore	4	1 176	4	1 452	0%	0%	▼ -3%	▼ -19%
Norway	185	1 153	149	1 195	0%	0%	▲ 24%	▼ -4%
Finland	372	1 094	347	1 242	0%	0%	▲ 7%	▼ -12%
Malta	70	1 019	-	-	0%	0%	▲ 100%	▲ 100%
Estonia	355	1 008	323	1 147	0%	0%	▲ 10%	▼ -12%
Others	1 874	6 440	1 779	6 398	0%	1%	▲ 5%	○ 1%
Total	402 769	780 052	423 724	954 869	100%	100%	▼ -5%	▼ -18%

SOURCE: Import and export of drugs and medical devices in Uzbekistan

Table 3. Ratings of pharmaceutical manufacturers in Uzbekistan between 2013 and 2014.

No	Manufacturers	Amount	Amount of IUN	Average cost	Amount dynamics	Market share	Growth in amount	Packaging growth	Growth in cost
1	BERLIN-CHEMIE	55 291 978	29	4,0	- 14 127 972	6,1%	▼ -20%	▲ 2%	▼ -22%
2	SANOFI-AVENTIS	29 588 492	62	6,4	- 8 306 300	3,3%	▼ -22%	▼ -6%	▼ -17%
3	АРТЕРИУМ	26 992 974	43	3,7	- 18 175 352	3,0%	▼ -40%	▼ -29%	▼ -16%
4	WORLD MEDICINE	23 433 039	63	6,5	1 396 330	2,6%	▲ 6%	▲ 34%	▼ -20%
5	KRKA D.D.	21 209 245	44	3,0	- 7 557 051	2,3%	▼ -26%	▼ -6%	▼ -21%
6	ОТЕЧЕСТВЕННЫЕ ЛЕКАРСТВА ОАО	19 330 459	23	3,0	- 634 550	2,1%	▼ -3%	▲ 19%	▼ -18%
7	NOVARTIS	18 789 418	53	5,0	- 12 056 792	2,1%	▼ -39%	▼ -28%	▼ -15%
8	DENTAFILL PLYUS ЧП	18 180 757	54	0,5	- 5 534 108	2,0%	▼ -23%	▼ -13%	▼ -12%
9	БОРИСОВСКИЙ ЗАВОД МЕДПРЕПАРАТОВ	17 848 463	73	0,6	10 786 651	2,0%	▲ 153%	▲ 6%	▲ 138%
10	TAKEDA	17 305 806	24	6,1	- 7 068 972	1,9%	▼ -29%	▲ 8%	▼ -34%
11	GEDEON RICHTER	17 124 396	57	3,8	3 749 885	1,9%	▲ 28%	▲ 68%	▼ -24%
12	UNIPHARM, INC.	14 368 295	8	7,5	- 21 879 264	1,6%	▼ -60%	▼ -46%	▼ -27%
13	ABBOTT	14 007 329	22	10,4	- 3 365 146	1,5%	▼ -19%	▼ -1%	▼ -19%
14	GM PHARMACEUTICALS LTD	13 946 624	30	5,1	- 3 016 890	1,5%	▼ -18%	▼ -9%	▼ -10%
15	MARION BIOTECH PVT. LTD	13 299 756	12	2,8	- 7 197 674	1,5%	▼ -35%	▼ -23%	▼ -15%
16	NIKA PHARM ДХО	12 924 760	35	0,8	- 2 436 775	1,4%	▼ -16%	▲ 39%	▼ -40%
17	NOBEL	12 776 861	36	2,6	- 1 504 123	1,4%	▼ -11%	▲ 8%	▼ -17%
18	ФАРМАК ОАО	12 676 056	56	1,3	- 4 775 255	1,4%	▼ -27%	▼ -3%	▼ -25%
19	ЮРИЯ ФАРМ ООО	11 921 355	23	3,7	- 3 787 892	1,3%	▼ -24%	▼ -8%	▼ -18%
20	JACOBUS PHARM COMPANY INC	11 765 369	1	255,1	5 845 309	1,3%	▲ 99%	▲ 148%	▼ -20%
21	ДАРИ-ФАРМ ТОО	11 612 131	19	4,5	- 1 704 185	1,3%	▼ -13%	▲ 5%	▼ -17%
22	ФАРМСТАНДАРТ ОАО	11 505 847	50	0,5	- 854 789	1,3%	▼ -7%	▲ 17%	▼ -21%
23	AGIO PHARMACEUTICALS LTD	11 425 394	15	1,9	1 465 917	1,3%	▲ 15%	▲ 19%	▼ -4%
24	ЖУРАБЕК ЛАБОРАТОРИЕС ЛТД СП	11 344 911	21	0,8	- 8 389 884	1,3%	▼ -43%	▼ -25%	▼ -23%
25	СИНТЕЗ АКО ОАО	11 325 009	36	1,0	452 797	1,3%	▲ 4%	▼ -7%	▲ 12%
26	МИНСКИНТЕРКАПС УП	9 667 607	11	2,3	3 118 117	1,1%	▲ 48%	▲ 79%	▼ -18%
27	MERRYMED FARM СП ООО	9 626 471	32	0,3	- 1 076 350	1,1%	▼ -10%	▲ 1%	▼ -11%
28	PIERRE FABRE MEDICAMENT	8 955 273	19	5,4	- 995 368	1,0%	▼ -10%	▼ -5%	▼ -5%
29	REMEDY ООО	8 619 028	86	0,8	63 670	1,0%	▲ 1%	▲ 17%	▼ -14%
30	NOVO NORDISK A/S	8 482 336	9	11,5	- 11 344 895	0,9%	▼ -57%	▼ -60%	▲ 7%

Source of imports of drugs and medical devices in Uzbekistan

Furthermore, the modernization, technical and technological re-equipment of the pharmaceutical enterprises of the Republic of Uzbekistan for the period up to 2015 is aimed to upgrade industrial enterprises, fitting out them with modern high-tech equipment, the adoption of modern scientific achievements and advanced innovative technologies by attracting direct investment. From the

Table 3.7 it is obvious that the main importers are India (16%), Germany and Russia (11%), Ukraine (9%), China (5%), Belarus (4%), whereas, in real terms - Russia (30%), India (12%) and China (11%), Byelorussia (10%) (Tab.3).

Berlin Chemie takes the first place with a market share of 6.1%. However, the year ended with 20% numbered to a loss of 14 million US dollars. The second rate is taken by Sanofi, the market share of which is 3.3%. Third place is related to the Ukrainian company Arterium with a share of 3%. Among the positive growing companies in the territory of Uzbekistan Borisov Medical Preparations Plant from Belarus may be noted with a well-developed product portfolio and a very low price for the product packaging (Tab.3).

In general, almost all of the first 30 companies completed 2014 year with negative figures in comparison with 2013.

3. The legal bases of pharmaceutical manufacturing

From the first days of independence, the government has been giving a special attention to the implementation of legal and administrative documents related to the public health care, diseases treatment and drug facilities [1].

In addition, a lot of Presidential decrees, resolutions and government programs are elaborated with the aim of improvement of health care system. According to these legal documents, large-scale work has been carried out on the primary health care evolvement, maternal and child health protection and other projects implementation. Moreover, the numbers of Presidential decrees and legal sanctions have been developed to reform the pharmaceutical system, as well as the quality of medical services and health care. Meanwhile, the fundamental document for all reformations was the law of the Republic of Uzbekistan "On drug facilities and pharmaceutical activity" from 25.04.1997 with amendments and complement in 1999, 2006 and 2009 [9].

The law gives a wide definition to the concept of "Manufacturing of drug facilities", which comprehends the serial production of medicaments in accordance with the rules of enterprises and quality control systems including the whole technological cycle or separate stages of production: synthesis

(biosynthesis), extraction, cleaning, processing, packing, packaging and labeling of medications etc.

Drugs and medical items manufactured by enterprises which have a license that gives the privilege to produce them. This requirement is consolidated by the Resolution of the Cabinet of Ministers of the Republic of Uzbekistan from 13.05.2010, №91 “On measures for further enhancement of pharmaceutical activity licensing order” [18].

In addition, according to the resolution of “On licensing certain types of activities” on June 28, 2002, № 236 the Pharmaceutical Licensing Board has been operating to create measures that implement the law of the Republic of Uzbekistan [6,16]. Today, the pharmaceutical licenses set out to economic entities are engaged in the following areas:

- The manufacture of medicines and medical items;
- The preparation of drugs and medical products;
- The scientific researches on the development of medicines and medical products;
- The quality control of medicines and medical products;
- The retail of drugs and medical products;
- The wholesale of medicines and medical products;
- The production, harvesting, manufacturing, packaging and wholesale of medicinal plants, animal and mineral based raw materials.

The development of domestic pharmaceutical industry is regulated by the following normative-legal acts. These documents, in accordance with which the Uzbek state joint stock concern of the pharmaceutical industry (Uzpharmprom) [8] was formed, as well as priorities of industrial development of Uzbekistan in 2011-2015 were defined, measures to further deepen the localization of production of ready products were outlined, items and materials based on industrial cooperation in 2011-2013 [9] were replenished, the program of priority measures to increase production volumes and the evolvement of new types of competitive products [2] were formulated, additional measures to

augment production and expand the range of domestic consumer goods [13,15] and the program of modernization, technical and technological re-equipment of the pharmaceutical industry for the period until 2011 [14] were proposed.

Privileges and measures to support the domestic manufacturers are presented in the following legal documents. These documents define the measures of state support for the development of medical and pharmaceutical industry, regulation the import of ready medicines [24], and medicinal products' list for import which are not covered by tax exemption on value added tax [19]. Moreover, the raw material list for the production of medicines and medical devices was defined which is free from payment for the import of value added tax [11], and measures for the further development of industrial cooperation, and increment of export capacity [5].

Questions of quality guaranteeing are regulated by the following normative-legal acts, which have fixed the legal framework for ensuring the uniformity of measurements [21], product certification [20], standardization [5,17], ensuring a state control on quality of drugs, medical devices and therapeutic products of preventive nutrition [4,21].

Sphere of ready products is regulated by the following normative-legal documents, which have established the legal framework in promoting the distribution of medicinal products [13], additional measures to saturate the domestic market with drugs and medical devices [10], to further expenditure the range and volume of drug production and medical devices [12], as well as the advertising of medicinal products [3].

State regulation of prices for drugs is inseparably linked, especially economically, with a tax-exempt status of pharmaceutical and pharmacy enterprises, as well as financial support [7,15]. Price formulation and cost savings are regulated by the following legal documents, in order to establish the size restrictions on price markup not higher than 20% in the wholesale of medicines and medical products, in retail - not above 25% (26.24), as well as

introduce additional measures to reduce productive costs and prime costs in the industry [22,23].

4. Determination of tablets as dosage form.

Tablets (Tabulettae, from lat. Tabula - board, tabella - plank, tile) – the dosage form obtained by compressing a mixture of drugs or drug substances and excipients, tablets are used for indoor, outdoor, sublingual, implant or parenteral administration [25].



First Avicenna mentioned dosage forms such as lozenges (which are the prototype of modern tablets) in “Canon of Medicine”, which, depending on the purpose and dosage divided into dosage forms for immediate use, for storage and later use.

The first information about the pills belongs to the middle of the 19th century. In 1844 Brokedon received a patent in England for the tablet preparation of potassium hydrogen by pressing. In the years of 1846-1897 the production of tablets has been established in the USA, France and Switzerland. In Russia, the first major tablets workshop was opened in 1895 at the factory of military medical harvested in St. Petersburg. In 1900 member of “In stock with molded medicines at the pharmacy field pharmacy department of factory military medical harvested” Professor L.F.Ilyn wrote his first thesis “On compressed tablets or medicines”. In 1901, the first tablet dosage form was included in the Swedish Pharmacopoeia [28].

Tablets produced by the chemical and pharmaceutical industry, constitute approximately 40% of the production of finished drugs. Worldwide manufacture of tablets is increasing annually by 10-15%. Tablet dosage form is widespread throughout the world. Currently tablet formulations comprise about 80 % of the total volume of proprietary medicines [26,35]. Positive qualities tablets are: appropriate level of mechanization at the main stages and operations to deliver high performance, clean and hygienic production of these drug forms;

- accuracy of dosage in tablets;

- portability of tablets, providing the convenience of their release, storage and transportation;
- drugs prolonged preservation in the pressed state;
- for unstable substances - the possibility of applying the protective shells;
- the possibility of masking unpleasant organoleptic properties (taste, smell, colored powder);
- combination of medicinal properties that are incompatible on physico-chemical properties in other dosage forms;
- containment of drug substance in a certain part of the gastrointestinal tract by coating shells that soluble in acidic or alkaline medium;
- prolongation of action of drugs (defined by applying coatings, using special technology and composition tablets cores);
- regulation of sequential absorption of several drugs from pills at certain intervals (multilayer tablets);

However, tablets have some disadvantages:

- effects of drugs in tablets are relatively slowly;
- you can't enter the tablet with vomiting and swoon;
- when storing the tablets can be cemented, it increases the disintegration time;
- member of the tablets may contain excipients that have not therapeutic value, and sometimes cause some side effects (e.g., talc irritates the lining of the stomach);
- individual drugs (e.g., sodium or potassium bromide) in the dissolution zone to form highly concentrated solutions, which can cause severe irritation of the mucous membranes (this drawback is eliminated by dissolving the tablets in a certain amount of water);
- not all patients, especially children, are easily swallow pills.

Tablets are classified as on design features:

1. By composition: simple (one-component) and complex (multi-component).

2. By structure: element, monolayer and multilayer (not less than 2 layers), with or without a coating.

Frame (or skeletal) tablets (duruls) are insoluble frame voids are filled with the drug substance. Separate tablet is like a sponge soaked in medicine. When receiving a frame it is not soluble, retaining its geometrical shape, and the drug diffuses into the gastrointestinal tract [26].

Single-layer tablets consisting of compressed mixture of drugs and excipients and uniform throughout the volume of the dosage form.

3. By the nature of the coating: sugar-coated, film and pressed powder coating.

Form of tablets produced chemical and pharmaceutical industry - the most diverse: cylinders, spheres, cubes, triangles, rectangles, etc. The most common form of valium is chamfered and lenticular shape for comfortable swallowing [32].

Most of the filling and packaging machines are also adapted to work with valium and biconvex tablets. Valium without chamfer form for the production of tablets is not recommended, since the packaging and transport of acute edges tablets observed destruction, resulting in lost their marketability [38].

Tablet size ranges from 4 to 25 mm in diameter. The most common are tablet diameter from 4 to 12 mm. Tablets with a diameter of more than 9 mm, have one or two risks applied perpendicular to one another, allowing to divide the tablet into two or four parts, and thus to vary the dosage of the drug substance [39].

5. Drugs contain the complex substances of 3d metals

Synthesis and comprehensive study of the various types of coordination compounds biometals with vitamins and their derivatives is one of the rapidly developing areas of inorganic chemistry, promising to the creation of new drugs with desired pharmacological properties [51,52].

Coordination compounds 3d physiologically active metals with organic ligands have usually low toxicity and high biological activity, due in particular

to the fact that they act as a structural fragment of many natural biocatalysts [49].

In addition, synthesized in recent years and introduced into medical practice medicinal products on the basis of coordination compounds biometals and physiologically active ligands, such as “Feramid”, “Cupir”, “Pyracin”, “Cogistin”, “Cobavit”, “Cobafitin”, “Ferasc” and others, show that in this area all potentialities for new biologically active compounds with desired properties [50].

Ferasc – used in hemorrhagic anemia (decreased hemoglobin content in the blood as a result of blood loss), iron-deficiency anemia (reduced hemoglobin in the blood as a result of violations of receipt, assimilation or isolation of iron) of different origin [58].



Maltofer – iron formulation drug that intended for oral administration. The preparation includes iron (III) hydroxide polymaltose complex, which prevents the appearance of prooxidant properties of iron. After absorption of drug into the systemic circulation from the iron ions are bound with haemoglobin. Iron accumulates in the body, primarily in the liver. The iron part of hemoglobin, myoglobin and various enzymes. The drug is used for the treatment of patients with iron deficiency anemia and latent iron deficiency. The drug may also be appointed by the attending physician for the prevention of iron deficiency in patients at risk, including elderly patients, pregnant women, patients who adhere to a strict diet, as well as in children and adolescents in the period of active growth [59].



Sorbifer-durules – antianemic drug, achieved by the combination of iron (Fe sulfate) and vitamin C. The preparation is made by a special technology durules that provides uniform and gradual release of iron ions from the special matrix. This feature eliminates the possibility of drug sharp increase the iron content in the digestive tract that leads to the



absence of irritating action of iron ions to the mucosa of the digestive system [60].

Cupir – used in toxic and allergic reactions to background isoniazid, vitiligo (in combination with the Integrated photochemotherapy). Connection of pyridoxine and Cu^{2+} affects the intensity of metabolic processes, has antitoxic properties (isoniazid intoxication derivatives), increases the production of melanin [61].

Pyracin - the drug has clear hypolipidemic and anti-atherosclerotic activity. Drug is consumed in hyperlipidemia and atherosclerosis in peripheral blood cholesterol, total lipids, triglycerides, low density and very low lipoproteids, to reduce the amount of lipid peroxide oxidation products, and to increase the amount of high density lipoproteids and phospholipids [62].

Cobavit – used as a hepatoprotective agent in acute and chronic hepatitis of various genesis (including viral, toxic, reactive and medicines), liver cirrhosis, hepatomegaly posthepatitnoy; hepatopathy during pregnancy and chronic carriers of HBs-antigen.

Utilized as an antianemic agent in iron hypochromic anemia, anemia in pregnant women, nursing mothers, anemia, nutritional origin in children, anemia associated with deficiency of B_2 , anemia of mixed genesis, hypoplastic and hemorrhagic anemia, anemia caused by toxic substances and drugs [64].

Conclusion to the 1st chapter. The world pharmaceutical market was observed and consequently it was clarified that this sector have taken the second place in the global economy. For example, in countries such as Japan, USA, France, Switzerland, Belgium, Germany, the annual drug consumption per capita numbered to \$ 250. In a large group of countries like Sweden, Canada, Finland, Denmark, the Netherlands, Italy, UK, Spain, Portugal, Argentina, Greece, Ireland it varies in the range of 100-250 dollars. In Czech Republic,



Hungary, Poland, Russia, Bulgaria the expenditure of medicines does not exceed \$ 50-100. Also in our country pharmaceutical industry is blooming. Nowadays, there are 154 appropriate licensed ventures engaged in production of drug facilities and medical items in Uzbekistan. Leaders of the last 2 years in the development and introduction of new products are "Novopharma Plus", "Nika Pharm", "DentaFill Plus", "Nobel Pharmsanoat" and "Remedy Group", and it should be noted that 22 members of the "Uzfarmsanoat" SJS have the international quality certificate of ISO: "Novopharma Plus", "Nika Pharm", "Radiks", "Jurabek Laboratories", "DentaFillPlus", "Zamona Rano", "NASA", "Remedy", "Remedy group", "Uzgermed Pharm", "Samsun-Tashkent-Pharm", "Gufik-Avicenna", "Asia Trade", "Reka-Med Farm", "SAMO", "Elastikum", "Merrymed Farm", "Nobel Pharmsanoat", "Galenika", "Makrofarm-Optima", "Immunomed" and "Pharmed". Most of these enterprisers engaged in tablet manufacturing. In addition, some of them specialized in manufacturing original drugs contain with complex matters of 3d metals.

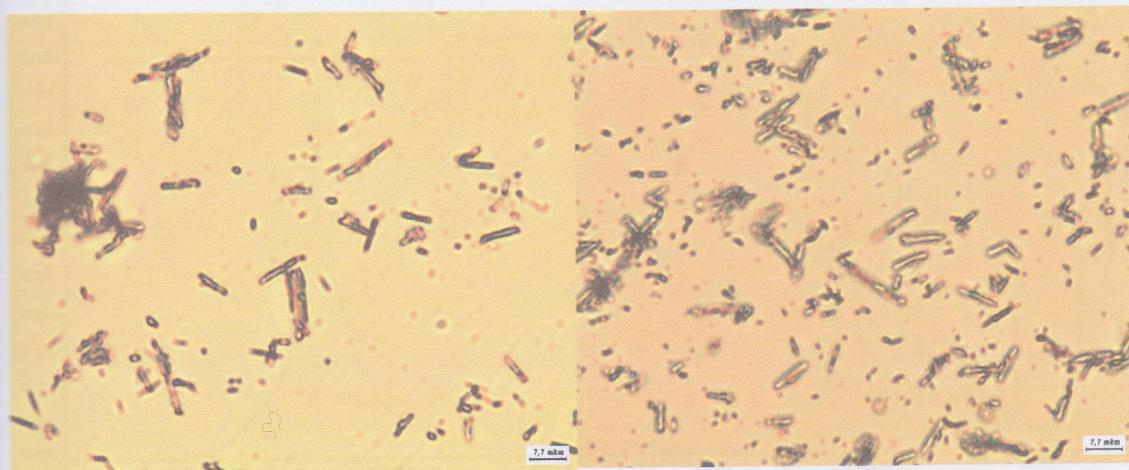
Figure 6. The size and the shape of researched crystal

CHAPTER II. PRACTICAL PART. PHYSICOCHEMICAL, TECHNOLOGICAL, BIOPHARMACEUTICAL PROPERTIES OF COMPLEX OF NICKEL WITH PYRIDOXINE AND NICOTINAMIDE

1. The physicochemical properties of the complex of nickel with pyridoxine and amide of nicotinic acid.

All cells and tissues of the human body contain the chemical elements in the state of free and as a set of chemical compounds. Medical properties of elements and their compounds are usually close or identical [34]. These compounds include complexes and components characteristic to a living organism. With the development of chemistry, scientists began to note that the action of, for example, metals may be enhanced with the formation of compounds with medicinal substances that are specific to one or another disease [40]. By the researchers of Tashkent pharmaceutical institute synthesized new complex matter of nickel with pyridoxine and nicotinamide, and studied the physicochemical property. The complex of nickel is light green colored fine crystalline powder, without a specific smell and taste. The size and the shape of the particles of powder have been studied in optical-spectral microscope in cooperation with the Republican Scientific Center of Polymer Chemistry and Physics. The results revealed that the size of particles is between 0.8-20 microns and powder crystals are in the form of rod (Fig.6).

Figure 6. The size and the shape of researched crystal



Solubility. Powder moderately soluble in water by forming an opalescent, which is practically insoluble in alcohol and ether. The structure of complex

decomposes under the impact of acid and alkali. Aqueous solution of drug is unstable.

Authenticity reactions. Authenticity of the complex is identified by several physicochemical methods. IR spectrum of complex was recorded in cooperation with a laboratory of Head department of quality control of drug facilities and medical items, in spectrophotometer of “Shimadzu” (Japan) in the region $4000-400\text{ cm}^{-1}$. Obtained IR spectrum serves as the structure identification analysis for complex (Fig.7).

In addition, the UV spectrum of the complex is registered in the scientific centre of drug standardization, in spectrophotometer “Agilent technologies” (Germany) in the region of $250-350\text{ nm}$. Thereto, 0.01 g powder of complex is weighed (accurate sample) and dissolved in the measuring flask with the volume of 100 ml with a mixture of 70% acetic acid and 96% ethyl alcohol in a ratio of $1:10$. The volume of solution reaches with above mentioned mixture and mixes. Solution filtrates over the paper filter (blue ribbon), throw off the first 20 ml of filtrate. 1 ml aliquot of the prepared solution is put into the measuring flask with the volume of 50 ml and the volume of solution reaches the mark with the former solution. The solution of complex gives the absorption at 289 nm (Fig.8).

Figure 7. IR spectrum of complex

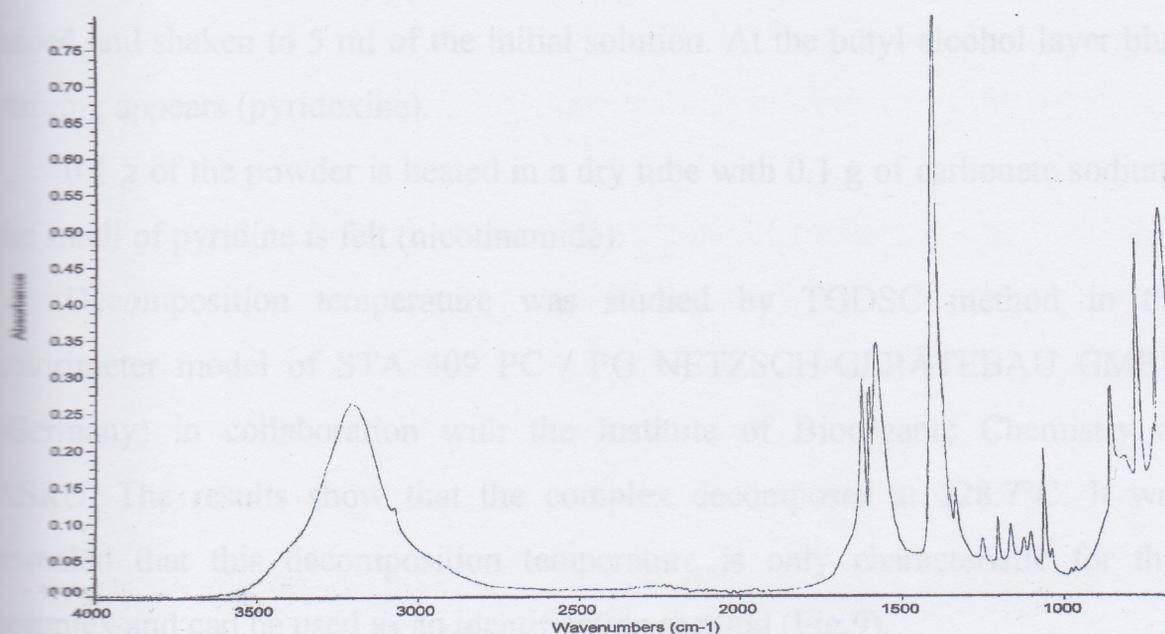
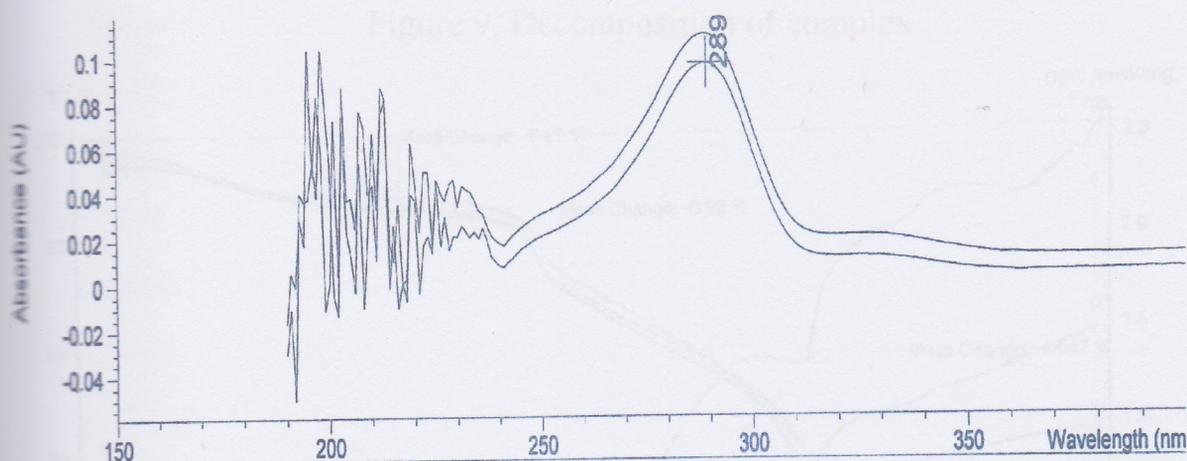


Figure 8. UV spectrum of complex



The pharmacopoeial reactions are conducted to identify the individual components of the complex [27,29,33,37,45,47,46].

0.2 g of powder is carefully dissolved in 20 ml of water and 5 ml of ammonia solution is added.

Reagent of Nessler is added to 5 ml of initial solution as a result red-tulip color appears (nickel).

To 2 ml of the initial solution 1 ml of silver nitrate is added, appears white precipitate which dissolves by the addition of ammonia solution (chloride).

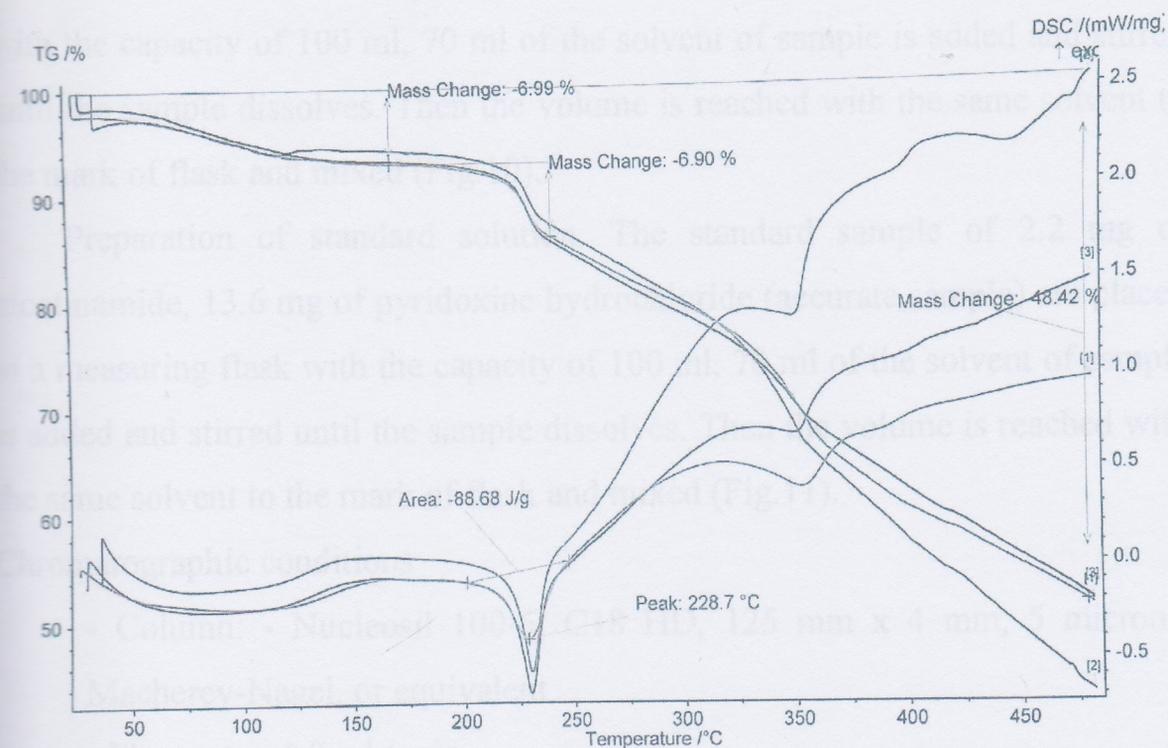
1 ml of ferric chloride is added to 5 ml of the initial solution, red color appears which is its turn disappears by adding diluted sulfuric acid (pyridoxine).

2 ml of a solution of 2,6-dichlorokinonchlorimid and 3 ml butyl alcohol is added and shaken to 5 ml of the initial solution. At the butyl alcohol layer blue staining appears (pyridoxine).

0.1 g of the powder is heated in a dry tube with 0.1 g of carbonate sodium, the smell of pyridine is felt (nicotinamide).

Decomposition temperature was studied by TGDSC method in the calorimeter model of STA 409 PC / PG NETZSCH-GERÄTEBAU GMBH (Germany) in collaboration with the Institute of Bioorganic Chemistry of ASRU. The results show that the complex decomposes at 228.7°C. It was revealed that this decomposition temperature is only characteristic for this complex and can be used as an identification method (Fig.9).

Figure 9. Decomposition of complex



Instrument	File	Identity	Sample	Date	Mass/mg	Segment	Range	Atmosphere	Corr.
STA 409 PC/PG	2.dsv	04-05-15	probe2	2015-05-05	9.300	1/1	23.0/5.0(K/min)/500.0	---/50 / ---/20 / ---/---	DSC:820/TG:020
STA 409 PC/PG	3.dsv	03-05-15	Probe3	2015-05-04	5.000	1/1	23.0/5.0(K/min)/500.0	---/50 / ---/20 / ---/---	DSC:020/TG:020
STA 409 PC/PG	1.dsv	1-05-15	farm_1	2015-05-01	6.100	1/1	23.0/5.0(K/min)/500.0	---/50 / ---/20 / ---/---	DSC:020/TG:020

Loss on drying is performed on moisture tester at 105°C for 5 minutes. Moisture content should not exceed 6.0%. As well as, the content of crystallization water has been studied by the method of Karl Fischer on the equipment of Titration Excellence Mettler Toledo (Switzerland). The amount of crystallization water should not exceed 6.0%.

The pH index of the solution is determined by the method of potentiometry on the pH meter Mettler Toledo (Switzerland). The pH index of the complex is between 5.3 and 6.5.

The quantity of nickel in the complex is determined by the method of chelatometry. 0.1 g preparation is put into a measuring flask with the capacity of 100 ml, add 5 ml of ammonia solution, 2 ml of murexide and titrates with trilon B till the yellow color of solution changes into violet.

Quantity analysis is performed by the method of HPLC. Chromatographic system: Apparatus: liquid chromatography with UV detector with variable wavelength.

Preparation of test solution. 26.1 g preparation is put into a measuring flask with the capacity of 100 ml, 70 ml of the solvent of sample is added and stirred until the sample dissolves. Then the volume is reached with the same solvent to the mark of flask and mixed (Fig.10).

Preparation of standard solution. The standard sample of 2.2 mg of nicotinamide, 13.6 mg of pyridoxine hydrochloride (accurate sample) are placed in a measuring flask with the capacity of 100 ml, 70 ml of the solvent of sample is added and stirred until the sample dissolves. Then the volume is reached with the same solvent to the mark of flask and mixed (Fig.11).

Chromatographic conditions

- Column: - Nucleosil 100-5, C18 HD, 125 mm x 4 mm, 5 microns, Macherey-Nagel, or equivalent
- Flow rate - 1.0 ml / min
- Column temperature - 40 °C
- Wavelength - 254 nm
- Introduction volume -20 µl

Mobile phase A. Acetonitrile for HPLC.

Preparation of buffer solution (mobile phase B). 0.05 M of buffer solution of potassium dihydrophosphate is prepared and pH is reached to 3.0 with the solution H_3PO_4 . The solvent of sample: Acetonitril+0.1 M HCl (30:70) (Tab.4).

Table 4. The gradient of mobile phase.

Time, in min.	Mobile phase A, %	Mobile phase B, %
0.00	10	90
5.00	30	70
10.00	50	50
12.00	70	30
15.00	70	30
18.00	10	90

Figure 10. Spectrum of researched substance

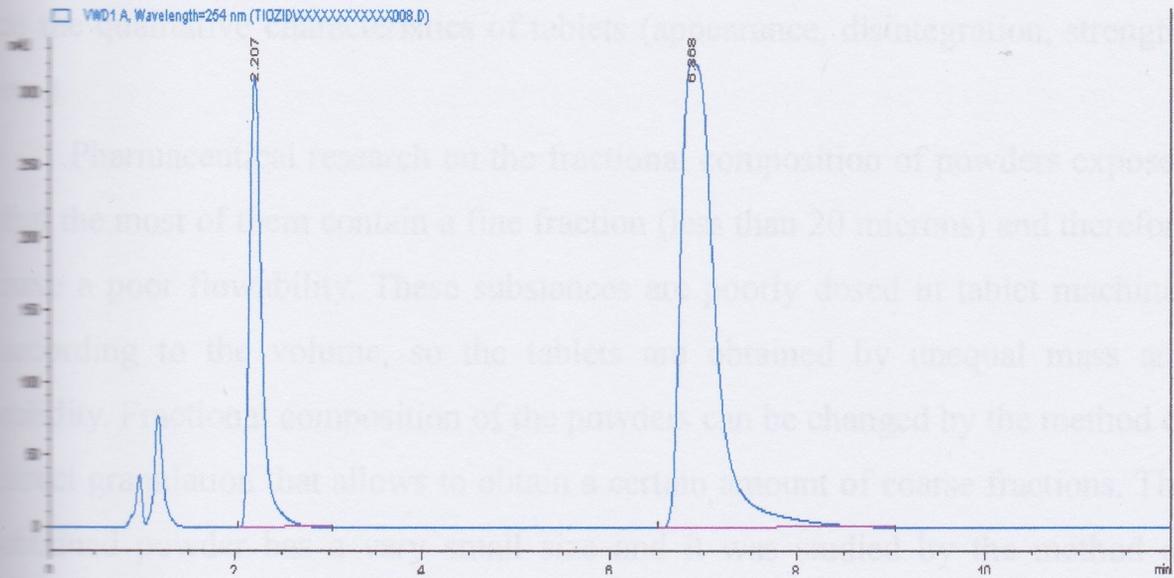
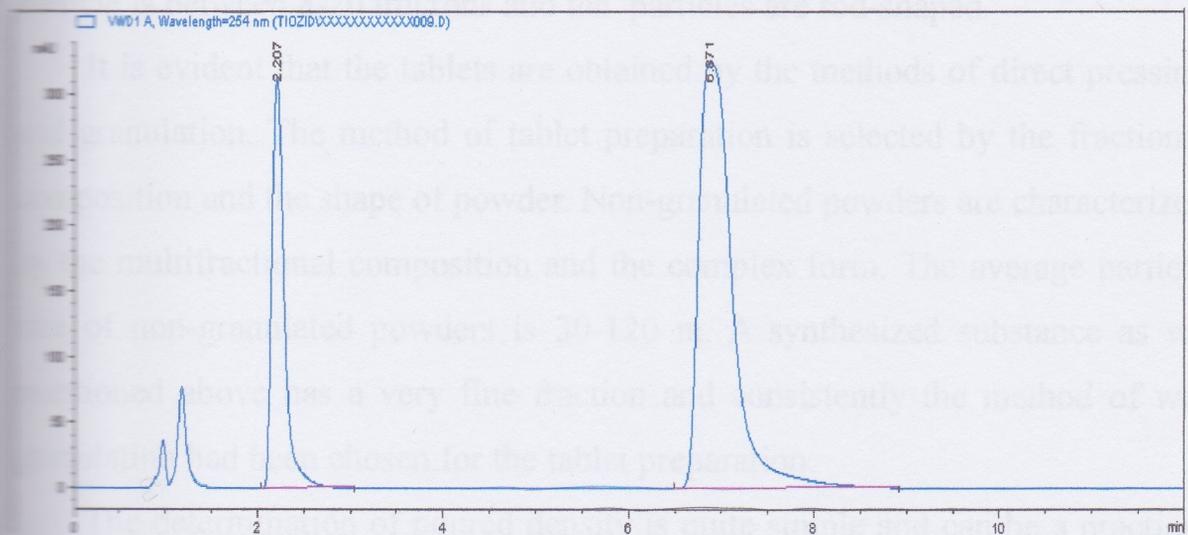


Figure 11. Spectrum of standard substance



2. Technological properties of the substance nickel complex with pyridoxine and nicotinic acid amide

Technological properties of powder-like medicinal substances include fractional (granulometric size) composition, apparent (bulk) density, relative density, porosity, compression coefficient, flowability (fluidity), compressibility, the strength of tablet ejection from the matrix, moisture content, dispersion and others. Flowability may be disrupted due to the sharp increase of internal

Fractional (granulometric size) composition is a distribution of powder particles according to their size. Fractional composition has a direct influence on the flow ability, consequently the rhythmic operation of tablet machines, the

stability of the tablet substances, the metering accuracy of drug facilities as well as the qualitative characteristics of tablets (appearance, disintegration, strength, etc.).

Pharmaceutical research on the fractional composition of powders exposed that the most of them contain a fine fraction (less than 20 microns) and therefore have a poor flowability. These substances are poorly dosed in tablet machines according to the volume, so the tablets are obtained by unequal mass and solidity. Fractional composition of the powders can be changed by the method of direct granulation that allows to obtain a certain amount of coarse fractions. The obtained powder has a very small size and it was studied by the method of electron scanning microscopy. The data showed that the size of a powder particle is between 8-20 microns and the particles are rod-shaped.

It is evident that the tablets are obtained by the methods of direct pressing and granulation. The method of tablet preparation is selected by the fractional composition and the shape of powder. Non-granulated powders are characterized by the multifractional composition and the complex form. The average particle size of non-granulated powders is 30-120 μ m. A synthesized substance as we mentioned above has a very fine fraction and consistently the method of wet granulation had been chosen for the tablet preparation.

The determination of poured density is quite simple and can be a practical indicator of powder properties, as well as it is a complex character that is dependent on the shape, distribution by the particle size, density, moisture content, powder dispersion and their specific surface. It is considered, that the bulk density affects to flowability. The researches show that by the increment of bulk density the powder flowability also improves. However, this is not the same in the finest fractions for which the relationship between the bulk density and the flowability may be disrupted due to the sharp increase of internal friction.

According to the bulk density powders are distinguished: very heavy, heavy, medium and light.

Bulk density was studied in a cylinder with a diameter of 25 mm and height of 24 mm. Cylinder was set on the parchment paper, filled with a studied powder. Then the powder was weighed with accuracy of 0.001 g on the electronic scale and obtained data was applied to the formula. The bulk density of the powder is 87 kg/m³.

$$\rho_{\text{coy}} = \frac{m}{V}$$

Here: ρ_{coy} - bulk density, kg/m³;

m - weight of mass in the shape, g;

V - volume of shape ($\pi r^2 h$).

Porosity is a relative space volume (pores, cavities) between the powder particles.

Compaction coefficient – the ratio of the powder height in the matrix to the height of the resulting tablet.

The particle shape affects the ability of compression of the powdered drugs, hence to the determination under the influence of pressure. Compaction ratio is an important technological factor. The more greater the compression rate, the more time is spent on compression, thus more effort is expended to push out the tablets from the bottom of the matrix hole.

To study the compaction coefficient of the researched powder the 0.5 g of this substance is compressed under the pressure of 1200 kg/cm², in the special matrix with a diameter of 11 mm and a height of 22.3 mm, compaction ratio is 3.29 K.

The flowability and the compressibility are the most important technological properties of drugs in tablet compression.

The flowability (fluidity) - the ability of flowing of the powder from the capacity or fluiding under the gravity and ensuring a steady filling of the matrix hole. A material having poor flowability may stick to the walls of the tableting machine bunker through which the substance enters into the matrix, and disturb the operation rhythm leading to oscillations in tablet mass and density.

There to, 50.0 g of powder was weighed with an accuracy of 0.001 g in the electronic scale. Powder was put into the funnel of apparatus, whereas a device was plugged into the mesh. At this point, the vibration compacted the powder for 20 seconds. After that, the bottom of the funnel was opened and observed the full time for a total flow of powder. The experiment was repeated for 5 times. Results put into this formula and flowability of powder numbered to $19.53 \text{ g/s} \cdot 10^{-3}$.

$$V_{\text{flow}} = \frac{m}{t - 20}$$

Here V_{flow} - flowability of substance, $\text{g/s} \cdot 10^{-3}$;

m - average mass of powder, in g;

t - time for total flow of substance, second;

20 - time for compression of mass, second.

The powder flowability (fluidity) is a complex characteristic determined by a number of factors: the particle dispersion and shape, moisture content of powder, granulometric size, as well as the interparticle and external friction. These factors are associated with contradictory relationship. For instant, by the increase of the particle size the fluidity also increases, but at the same granulometric fraction the particle size will not be the same, due to the difference in the specific surface. Almost in all cases, the fluidity of the powders, determined by the outflow time of powder from the funnel, falls with the decrease of particle size due to the growth of contact area. The spherical particles have a better flow property than others, e.g. needle or plate.

The reduction of the fluidity decreases the bulk density, but with linear bulk density the substance will show different fluidity, hence it depends on the shape of the particles and the coefficient of interparticle friction. The flowability is often determined by a rate of pouring out of a certain amount of substance in definite time (30-100 g) from a metal or a glass funnel with strictly prescribed geometrical parameters and the angle of repose.

Compressibility - the ability of powder particles towards a cohesion under

the pressure, i.e. the ability of the powder particles to form a stable compression under the influence of electromagnetic forces of nature (molecular, adsorption, electrical) and mechanical linkages to the mutual attraction and cohesion. Therefore, the particles of powder seal, adhere and create bonds to each other to form a homogeneous matter.

For determine the compressibility of the researched powder, 0.5 g (accurately weighed) of powder is compressed under the pressure of 1200 kg/sm² at the hydraulic press and in the matrix with a diameter of 11 mm. The height and weight of resulting tablet were measured and data were applied to the definite formula. Compressibility of powder is 10 N.

Compressibility also can be measured by the compressive strength of the tablet. Compressibility is characterized by the strength of the model tablet after the pressure relief. If the compressibility of the powder is in a good quality, the durability of tablets will also be higher. If the compressibility is low, the tablet will be fragile and sometimes completely destroyed by pushing out from the matrix.

The above-described technological characteristics of the powdered drug substances have the utmost importance in composition development and tablet technology, which must ensure the necessary bioavailability and consequently efficacy and safety of drugs. Technological characteristics of the powders are quickly identified, the methods of their determination are simple and do not cause problems, so these techniques are now widely used in the pharmaceutical industry for mass control of all drug substances. Typically, in pharmaceutical plants the dispersion analysis of the drug substances is carried out by available methods such as sieve analysis, microscopy, using a laser particle size analyzer, etc. This allows to exclude the out-of-order substances from pharmaceutical manufacturing at the stage of selection of medicinal substances suppliers and provide high-quality of domestic tablet formulations. The results of all experiments collected and introduced in the form of table to make convinience for the readers (Tab. 5).

Table 5. The results of technological properties of powder.

No	Studied rates	Measurement unit	Results
1	Shape of particles	mcm	rod
2	Flowability	kg/s * 10 ⁻³	19.53
3	Bulk density	kg/m ³	87
4	Compression	N	10
5	Compaction rate	K	3.29
6	Moisture content	%	6.0
7	Moisture absorption	%	1.4-2.2%

3. The results of biopharmaceutical research of complex matter

The research of new therapeutic agents that include organic compounds still remains as a main focus of modern pharmacology. Studies of last years have shown the availability of creating original drugs that based on metal complexes. The fruitfulness of the usage of complex matters as drugs is confirmed by many examples [43].

It is known, that the set of biological effective elements and pharmacological active ligands in complex compounds in many cases lead to a decrease of toxicity and increment of activity, relatively to biogenic effectiveness of metal ions and their organic salts.

Nickel refers to the metals that activate enzymes [51]. Microflora of gastrointestinal tract contains a number of enzymes, which are found nickel [42].

In the early 20th century, it was found that the pancreas is rich in nickel. When nickel is administered after insulin, it prolonged the action of insulin, thus the hypoglycemic activity is increased [41].

In the functional changes of liver, the marked changes occur in the microelement spectrum of blood [52]. Moreover, the amount of nickel declines in liver cirrhosis, when only traces of nickel are found in the blood. The changing of microelements' content in the blood was observed in all patients with coronary heart disease.

There were occurred some pathological changes in the liver by the decline of nickel content in the body: decrease of organs size, glycogen content reduce, activation of lipid peroxidation. By the supplementation of inorganic nickel salts in animals' food allowance in the amount of 50-80 mg/kg per day these symptoms are eliminated or prevented their development. However, because of the high toxicity and low biological activity of inorganic salts of nickel, they are not widely used in medicine, so the synthesis and study of coordination compounds of nickel that have lower toxicity and wide biological activity is an actual problem of pharmacology and make a great contribution to theoretical and practical interest in research on new physiologically active substances. Hence, we performed the intentional synthesis of complex compound of nickel with pyridoxine and amide of nicotinic acid.

Pharmacological studies of the complex. The general effect and toxicity of the complex was studied in laboratory mice weighing 18-22 grams of either sex kept in the normal diet of the vivarium. The drug was administered orally by a metal probe in doses of 50-100 mg/kg and consequently 250-1000 mg/kg. Research had shown that there was not provoked any adverse reaction in animals when the drug administered to mice in doses of 50-100 mg/kg. There were a slight decrease in locomotive activity and insignificant acceleration of the breath frequency, as well as tachycardia when the dosage of preparation is augmented to 250-1000 mg/kg. Some of mice died 2.5-3 hours after the administration of drug.

After the statistical processing of the results we found that the LD_{50} of tested compound is equaled to 799.5 (673.4 ÷ 948.7) mg/kg.

On the study of the drug impact on respiration and blood pressure, the preparation was input orally at a dose of 30-50 mg/kg. It was found that the drug slightly and briefly decreased the blood pressure (15-30 mm. of mercury), while respiration is not changed significantly.

The effect of the drug on the isolated intestinal spasm was examined in further studies that induced by barium chloride at a concentration of $2 \cdot 10^{-4}$ g/ml. The drug was administered orally to experimental animals in the same conditions and studied the effect of the drug on the tonus and contraction amplitude of intestine. It was revealed that the preparation reduced the intestinal spasm to 15-20% at a concentration of $2 \cdot 10^{-3} - 1 \cdot 10^{-3}$ g/ml.

In individual series of experiments the effect of the drug on the strength and duration of the sedative effect of hexenal (70 mg/kg, intraperitoneal) and chloral hydrate (300mg/kg intraperitoneal) was examined. It was found that the drug at a dose of 25-50 mg/kg significantly increased the sleep time - at 17-28% and 21-42%, respectively. The drug markedly shortens the latent period of the onset of sleep.

The effect of the drug on hematopoiesis was studied by determining the number of reticulocytes in peripheral blood. It was established that the drug administrated orally at a dose of 15 and 25 mg/kg increased the amount reticulocytes to 155-171% in the peripheral blood. Furthermore, the studied drug in doses of 25 and 50 mg/kg significantly stimulated hematopoiesis. On the 10th day the number of red blood cells and white blood cells is increased markedly in peripheral blood, but the amount of hemoglobin is remained at the level of the physiological norm (Tab. 6).

The effect of the drug on diabetes was carried on in the experimental conditions on rats weighing 160-187 g of both sexes. The hypoglycemic activity of the preparation was investigated by experimental hyperglycemia was induced with intraperitoneal injection of a hypertonic glucose solution at a dose 4.5 g/kg.

In individual series of experiments the effect of the drug on the strength and the duration of sedative effect of hexenal (70 mg/kg, intraperitoneal) and

chloral hydrate (300mg/kg intraperitoneal) were examined. It was found that the drug at a dose of 25-50 mg/kg significantly increased the sleep time - at 17-28% and 21-42%, respectively. The drug markedly shortens the latent period of the onset of sleep.

Table 6. The impact of preparation to the peripheral blood condition

№	Blood rate	Initial data	The peripheral blood condition after the drug administration, in			
			10 days		21 days	
			Control	25 mg/kg	Control	25 mg/kg
	Hemoglobin in %	12.6±0.25	12.5±0.25	12.7±0.40	11.9±0.35	12.5±0.51
	Erythrocyte in mln.	5.5±0.31	5.6±0.25	6.7±0.45	5.3±0.35	6.75±0.35
	Leukocyte in thous.	8.6±1.2	9.0±1.1	12.0±0.90	8.8±0.85	12.3±1.0

The studied medication was administered orally at the dosage of 25 and 50 mg/kg, 45 minutes before the input of glucose. By the enzymatic method the level of sugar was determined at 60 and 120 minutes.

It was found that the drug showed a significant hypoglycemic effect - at a dose of 25 mg/kg in 60 minutes the drug reduced the blood sugar levels by 32.1% (Tab. 7). Thus, we can suppose the drug reveals a pronounced hypoglycemic effect.

Table 7. The influence of drug to the blood sugar level of rats

№	Group of animals	Initial rate of sugar on blood, in		Dose of preparation	The amount of animals in	The rate of sugar in blood after			
		mmol e/l	%			60 minutes, in		120 minutes, in	
						mmole/l	%	mmole/l	%
	Control 1	4.2±0.5	100	1ml dist. water	7	7.6±0.63	180.9	5.3±0.3	126.2
	Preparation	4.2±0.5	100	25 mg/kg	7	6.25±0.3	148.8	4.55±0.3	108.3

Determination of microbiological purity and activity of the drug. For determining the microbiological purity 1 g of substance was diluted with 10 ml of sterile saline solution and obtaining solution mixed until getting a single phase. Sterile meat peptone agar, which is heated in advance at 45 °C mixed with 0.5 ml of previous solution. The obtained mixture was placed in a petri dish and incubated at 37 °C. The microbiological purity of the complex was determined in accordance with the number of colonies in solid medium. The purity index is observed for 7 days.

The next test was the identification of microbial activity of a substance by diffusion method. The meat peptone agar and Soburo were selected as the medium for microorganisms. Into sterile Petri dish molten growth media is spilled. The microorganisms were inoculated by the method of lawn.

Table 8. The inhibition zones in certain microorganisms

N_o	Test-strains	Hole zones (in mm)
1	Escherichia coli	32 mm
2	Staphylococcus aureus	15 mm
3	Candida albicans	22 mm
4	Pseudomonas aeruginosa	12 mm
5	Bacillus cereus	25 mm
6	Bacillus subtilis	30 mm

The certain bacterium was added to the nutrient medium that ensured the optimal growth and clarity of growth inhibition zones. After the solidification of the agar the holes in diameter of 6 mm was cut (for 1 cup of no more than 6 holes), consequently the tested solution of the drug was put an equal volume of in each of them (the concentration of 1 ml/g). Petri dishes were incubated in the incubator at 37 °C for 18-24 hours, than the diameter of growth inhibition zones in a round hole was measured (Tab. 8).

Conclusions to the 2nd chapter. New complex matter is light green colored fine crystalline powder, without a specific smell and taste. The crystal is

rod shaped and size is between 8-20 nm. The IR-spectrum, UV-spectrum of this complex is identified, as well as the decomposition temperature of matter is studied by the method of TGDSC. The solution of complex gives the absorption at 289 nm, whereas the decomposition temperature numbers to 228.7. The pH of the complex is between 5.3 and 6.5. The method of HPLC was chosen as a quantity identification method of complex. Technological properties of powder-like medicinal substances include fractional (granulometric size) composition, apparent (bulk) density, relative density, porosity, compression coefficient, flowability (fluidity), compressibility, the strength of tablet ejection from the matrix, moisture content, dispersion and others were determined. Certain pharmacological studies carried out in the central vivarium of Tashkent pharmaceutical institute. The effect of the drug on hematopoiesis was studied by determining the number of reticulocytes in peripheral blood. It was established that the drug administrated orally at a dose of 15 and 25 mg/kg increased the amount reticulocytes to 155-171% in the peripheral blood. The effect of the drug on diabetes was carried on in the experimental conditions on rats weighing 160-187 g of both sexes. It was found that the drug showed a significant hypoglycemic effect - at a dose of 25 mg/kg in 60 minutes the drug reduced the blood sugar levels by 32.1%. The microbiological purity and activity were studied and results showed that substance has different microbial activities.

average weight of tablets (Tab. 9).

According to the results in the table 3 we can conclude that model tablets in average weight of 0.35 g and made from three fillers had shown the similar index of strength. Despite of the strength index was increased in the following weights on model tablets which is made from microcrystalline cellulose, the tablets produced with calcium carbonate and bentonite showed unchanged strength index.

To sum up, to develop the new composition for pylicent substance all researched fillers were suitable to improve the technological properties of

CHAPTER III. OBTAINING TABLET DRUG FORM FROM COMPLEX MATTER OF NICKEL WITH PYRIDOXINE AND AMID NICOTINIC ACID

I. The amount and type of the auxiliary substances for tablet producing.

This is evident that tablet drug form is obtained by two methods: direct compression and granulation. Previous studies of the technological properties of researched substance have shown that substance has unsatisfied properties. Therefore, the method of wet granulation was chosen as a method of tablet producing.

For verifying the scientific basis of auxiliary matters, first of all we have chosen the most suitable filler to improve the negative technological properties of substance.

Therefore we used the index of Gandel to identify the rate of strength, consequently calcium carbonate, microcrystalline cellulose and bentonit were chosen as fillers to amend the technological properties of researched matter. 1 tablet consists of 0.25 g active substance and by mixing with fillers in the amount of 0.05, 0.10, 0.15, 0.20, 0.25 and 0.30 the model tablets with average weight of 0.3, 0.35, 0.40, 0.45, 0.50 and 0.55 were obtained, hence the fracture strength was determined and results were defined from the proportion of them to the average weigh of tablets (Tab. 9).

According to the results in the table 3 we can conclude that model tablets in average weight of 0.35 g and made from three fillers had shown the similar index of strength. Despite of the strength index was increased in the following weights on model tablets which is made from microcrystalline cellulose, the tablets produced with calcium carbonate and bentonite showed unchangeable strength index.

To sum up, to develop the new composition for pyrnamic substance all researched fillers were suitable to improve the technological properties of tablet.

Table 9. The results of selection of the fillers' type and amount according to the V.G.Gandel's strength index

Active substance	Studied compositions						
	1	2	3	4	5	6	7
Active substance, mg	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Excipient, g	-	0.05	0.10	0.15	0.20	0.25	0.30
Average weight of tablets, g	0.25	0.30	0.35	0.40	0.45	0.50	0.55
Calcium carbonate							
Breaking strength, kg	2.0	3.0	4.0	4.0	4.2	4.5	4.8
Strength index	8.1	10.9	11.8	10.2	9.6	9.4	8.7
Microcrystalline cellulose							
Breaking strength, kg	2.0	3.0	4.5	5.5	6.5	8.0	9.0
Strength index	8.3	10.4	12.8	13.9	14.8	16.7	16.9
Bentonit							
Breaking strength, kg	2.0	3.0	3.5	4.0	5.0	5.0	5.0
Strength index	8.7	10.3	11.3	10.3	10.3	10.3	9.9

To pick up the type and the amount of binders we tried to produce compression mass by using certain binders: 96% ethanol, 1, 3, 5% gelatinized starch, 1 and 2% gel of methylcellulose, sugar syrup and saturated solution of polyvinylpyrrolidone. However, after the utilization of some binders we have gotten the compressed mass with insufficient particle size and shape. Thus, the

properties of granulated mass which is in preparation used binders like ethanol, 5% gelatinized starch and saturated solution of polyvinylpyrrolidone could be identified (Tab.10)

Table 10. The influence of binders to the technological properties of substance

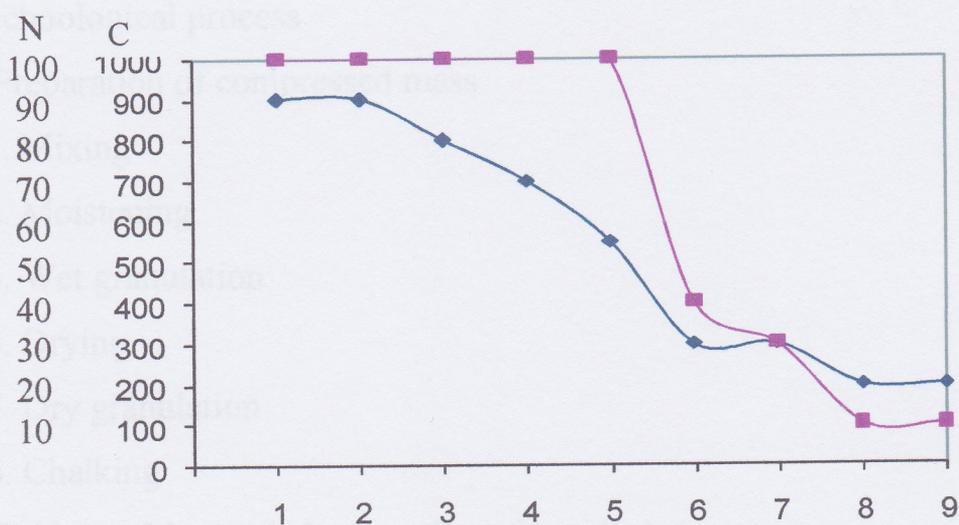
№	Studied rates	Measurement unit	Binders		
			Ethanol 96%	5% gelatinized starch	Saturated solution of polyvinylpyrrolidone
1.	Fractional composition:	mcm, %	-	-	-
	-1000		7.2	1.6	33.2
	+1000 - 500		11.3	15.2	21.3
	+500 - 315		12.6	26.7	20.9
	+315 - 250		15.4	43.6	15.4
	+250 - 200		18.9	10.6	4.8
	+200 - 150		30.3	2.3	4.4
	+150 - 80 + 80		4.3	-	-
2.	Flowability	kg/s 10 ⁻³	2.65	3.05	3.48
3.	Apparent density	kg/m ³	342.6	370.4	397.2
4.	Compressibility	N	25	35	40
5.	Compression coefficient	K	3.6	2.87	3.4
6.	Moisture content	%	8.2	9.6	6.7

According to the table 4, the technological properties of mass which is made with the saturated solution of polyvinylpyrrolidone that used as a binder

were shown the highest result. In spite of the compression mass which is prepared with 96% ethanol and 5% gelatinized starch didn't lead any difficulties and inconvenience during the making granulation mass, the research showed that technological properties of mass revealed less satisfactory technological properties in comparison with mass which consisted of polyvinylpyrrolidone.

To disintegrate the tablets in the intestinal tract it should be contains from anti-bonding matters, especially, if the substance totally insoluble or partially soluble with water. Therefore, the quantity and the type of anti-bonding matters for tablets of pyrimicam were chosen according to the results of experiments.

For that reason, the mixture of calcium carbonate and pyrimicam was moisturized with the saturated solution of polyvinylpyrrolidone, dried and compressed after the adding the sodium hydrocarbonate and citric acid in ratio with mass (Fig. 12).



-- disintegration time of tablets in seconds;

-- strength index of tablets.

According to the line graph we can see that by the increment of anti-bonding matters the strength index and as well as disintegration time decreased. The amount of anti-friction substances was determined according to the standards of these matters. As an anti-friction substance we used the calcium stearate in the amount of 1% in ratio to the weight of compressed mass.

These operations have done in followed apparatus (Tab. 11).

2. The technology of tablet drug form from researched substance

The technological process of obtaining tablets consists of certain activities:

AW 1. Auxiliary works

AW 1.1. Preparation of manufacturing rooms

AW 1.2. Preparation of manufacturing apparatus

AW 1.3. Preparation of professionals

AW 2. Auxiliary works

AW 2.1. Preparation of raw materials

AW 2.2. Weigh

AW 2.3. Grind

AW 2.4. Sieve

AW 2.1.4. Preparation of useful substances for making binders

AW 2.1.5. Preparation of binder

TP. 1. Technological process

TP. 1.1. Preparation of compressed mass

TP. 1.1.1. Mixing

TP. 1.1.2. Moistening

TP. 1.1.3. Wet granulation

TP. 1.1.4. Drying

TP. 1.1.5. Dry granulation

TP. 1.1.6. Chalking

TP. 1.2. Tablet making and cleaning them from dust

TP. 1.2.1. Compression

TP. 1.2.2. Cleaning from dust

P.W.T. 1. Packaging, wrapping, transportation

P.W.T. 1.1. Packaging

P.W.T. 1.2. Wrapping

P.W.T. 1.3. Transportation

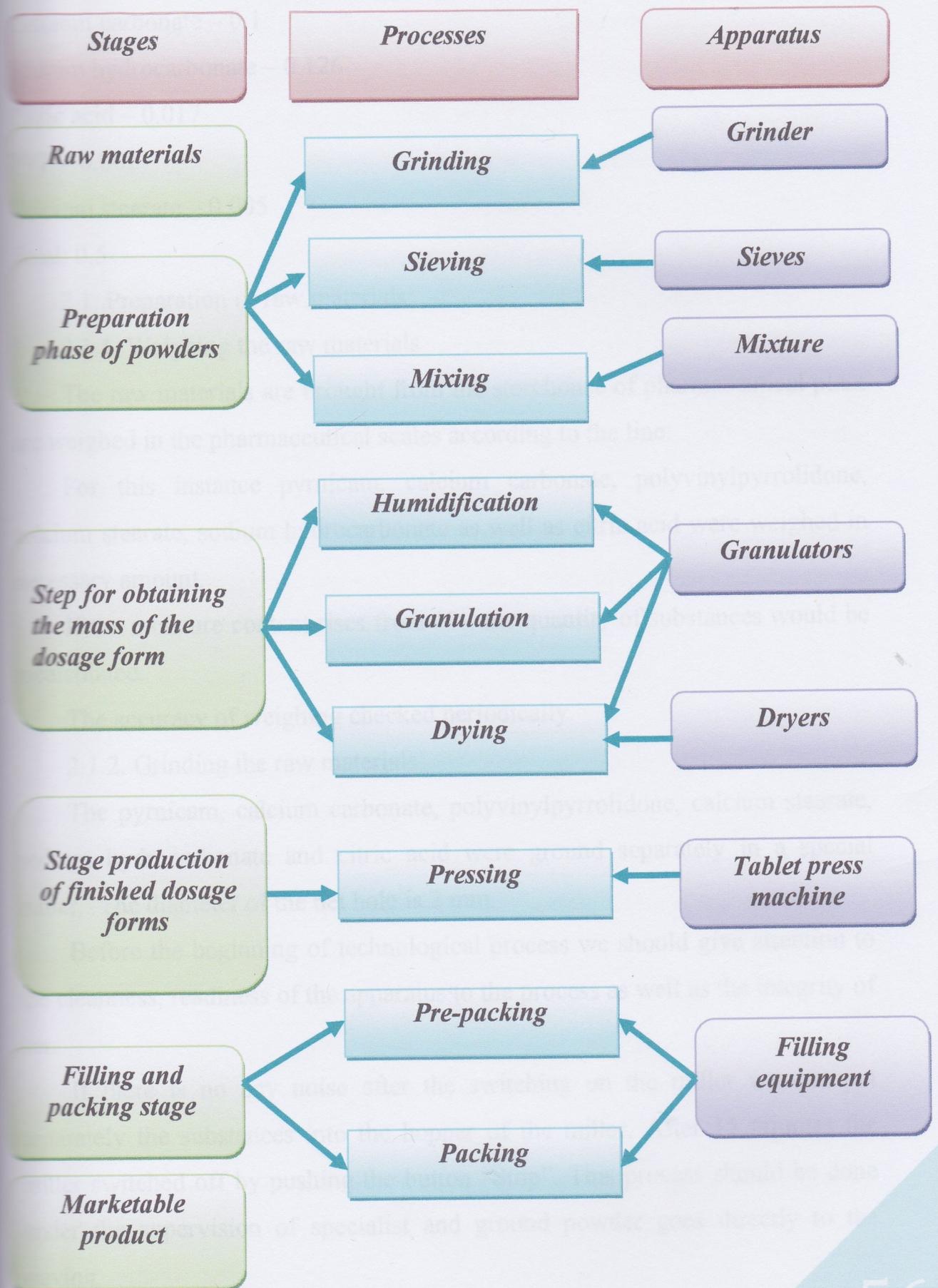
R.I. Recycling

These operations have done in followed apparatus (Tab.11).

Table 11. The list of tablet preparing apparatus and their characteristics

Process number	The apparatus name	Manufacturer	Efficiency of production
GP 1.	Medicinal scales	“Pribodetal” Orekhovo-Zuevo city, Type RI-150 kg	10-150 kg Inaccuracy 30 g
GP 2.	Vibrosieve	JZTO, type BC-2	80-40 kg/h
GP 4.	Sieve	TXFZ №32	
GP 7.	Mixer	“Krasniy Oktabr Fastov city”	50 l
GP 9.	Small cart	TXFZ 800x600x600 mm	
Sch 10.	Calorifer drying	“Korostenximash” E=10.5 m ² Ventilator calorifer type KOM	
GP 12.	Universal granulator	JZTO	400 kg/h
GP 14.	Tablet machine	JZTO Type RTM 41M2B	51-209 thousand of tablet/hour
GP 16.	Metal sieve TXFZ hole diameter 3 mm	TXFZ the hole diameter 3 mm	
GP 17.	Container	“Uzbekximash”	45 l
GP 18.	Package counter machine	JZTO SFM type	540-900 thousand of tablet/hour
GP 20.	“Servack” the automatic packaging line of tablets with the polymer film and foil	JZTO type 397-RK1	3600-7200 package/hour
GP 22.	Table		3000x1000 mm.

Figure 13. The technological scheme of manufacturing of "Pyrnicam" tablets



The Composition of “Pyrnicam” tablets

Pyrnicam – 0.25

Calcium carbonate – 0.1

Sodium hydrocarbonate – 0.126

Citric acid – 0.017

PVP – 0.002

Calcium stearate – 0.005

Total: 0.5

2.1. Preparation of raw materials

2.1.1. Weighing the raw materials

The raw materials are brought from the storehouse of pharmaceutical plant are weighed in the pharmaceutical scales according to the line:

For this instance pyrnicam, calcium carbonate, polyvinylpyrrolidone, calcium stearate, sodium hydrocarbonate as well as citric acid were weighed in necessary amount.

If the moisture content rises from 1%, the quantity of substances would be recalculated.

The accuracy of weighing checked periodically.

2.1.2. Grinding the raw materials

The pyrnicam, calcium carbonate, polyvinylpyrrolidone, calcium stearate, sodium hydrocarbonate and citric acid were ground separately in a special miller. The diameter of the net hole is 2 mm.

Before the beginning of technological process we should give attention to the cleanness, readiness of the apparatus to the process as well as the integrity of net.

If there is no any noise after the switching on the miller we can put separately the substances into the hopper of the miller. After 15 minutes the miller switched off by pushing the button “Stop”. This process should be done under the supervision of specialist and ground powder goes directly to the sieving.

2.1.3. Sieving the raw materials

Ground raw materials are sieved by the fosta nylon sieve №32. During the process of sieving specialists have to use gauze bandage and rubber gloves. This operation should be done under the supervision of specialists.

Sodium hydrocarbonate, citric acid and calcium stearate were sieved by vibrosieve. Before sieving the powders cleanness, readiness of the apparatus as well as the cleanness of hamper are checked. The ventilation system of equipment switched on and simultaneously the elasticity of net is checked.

Vibrosieve switched on by pushing the button "Activation". Sodium hydrocarbonate, citric acid and calcium stearate were put into the hamper by dividing into small parts. During the 10 minutes vibrosieve sieves the powders and this process controls by specialists, then sieved mass directly sent to the tablet making.

2.1.4. Preparation of the binder saturated solution of polyvinylpyrrolidone

Thereto, the necessary amount of polyvinylpyrrolidone weighed and mixed with pure water, solution left for 2 hours.

2.2. Preparation of compressed mass for tablet making

2.2.1. Mixing and moistening

Mixing process is performed in the special mixtures and this process is done in order to achieve smooth and uniform distribution of the active ingredient of tablets.

For mixing and moistening powders mixers of various designs are used:

- 1 Rotating blades;
- 2 Screw;
- 3 Blended drums.

When powders are mixing they must adhere to the following rules:

- 1 Add to much smaller;
- 2 Potent and toxic substances used in small amounts, pre-sieve, add mass at discrete portions as trituration, i.e. dilution concentration of 1:100;

3. Colored substance and the substance having a large specific weight put in the last instance into a mixer;
4. Volatile essential oils are input into a dry granular mass prior to the compression step dusts to avoid their volatilization.

Practice shows in the manufacturing operations of tablets, the time required to mix components the simple prescription (two - and three-component) in the dry state, is 5 to 7 minutes, for a more complex 10-12 minutes.

After mixing dry powders in mass batches moisturizer is added due to preventing its penetration.

In wet mixing uniform distribution of powders is greatly improved, there is no separation of the particles and the bundle of the weight, it improves the ductility. Stirring wetted powders accompanied by some mass due to seal air displacement, which allows obtaining more dense solid granules. Wet mass mixing time: for simple mixtures of 7-10 minutes for complex 15-20 minutes. The optimum amount of humectant is determined experimentally (based on physico-chemical properties of powders) and specified in the regulations. Error can lead to marriage if the amount of humidifier is small, the granules after drying will crumble if a lot of - mass will be viscous, sticky and poor granulation. Weight with optimal humidity of moist, compact the mixture does not stick to your hand, but disintegrating when squeezed into separate clumps.

Wet granulation method. The wet mass was granulated by special machines - granulators, the principle of which is that the material is rubbed blades resilient rollers or other devices over a perforated cylinder or grid. Granulators are vertical and horizontal.

Drying the wet granules. For this purpose there are various types of dryers:

1. Shelf dryer with forced air circulation;
2. Gel dryer column.

If necessary, the liquid contained in the material being dried, the dryer used in which air is passed through silica gel. In this valuable pair adsorbed, and the warm air was once used for drying material. As thermo-emitter in such

dryers are special reflector lamps, spiral filament placed at the focus of parabolic reflectors, metal and ceramic panel radiators with electric, steam or gas heating.

Freeze dryers. In recent years, the industrial application of the method was the drying of materials in a frozen state under high vacuum. It was called the freeze-drying or drying molecular. This method allows you to keep the quality of the underlying biological material to be dried. When this occurs the evaporation of a solid body without melting, bypassing the liquid phase.

Processing of the granules. In the drying process, the granules may separate from each other by sticking together in clumps. In order to ensure uniform fractional composition of dried the granules were passed through granulators nets with a mesh size of 1.5 mm, which is largely provides constant weight tablets. Thereafter, the pellets that dusted after adding the antifriction material, and transferred to the tablet step.

Structural granulation. It has a characteristic effect on the wetted material, which leads to the formation of rounded and sufficiently uniformly sized granules. Currently, there are three ways to granulation of this type used in pharmaceutical manufacturing: granulation coating pan; granulation in spray structural drying and granulation. For granulation in the coating pan is charged with a mixture of powders and during its rotation at 30 rev/min produce moisturizing binder solution feed through the nozzle. Powder particles clumped together, and dried with hot air due to friction become approximately the same shape. At the end of the granulation process is continued to drying glidantes.

Spray drying, granulation should be used in cases of undesired prolonged contact with air granulated product, if possible, directly from the solution (e.g., in the production of antibiotics, enzymes, raw products of animal or vegetable origin). A solution or suspension of the adjuvant and the humidifier and fed through nozzles into the chamber of a spray drier having a temperature of 150 °C. The atomized particles have a large surface, whereby an intensive mass and heat transfer. They quickly lose moisture and form in just a few seconds' spherical porous granules. The resulting granules were mixed with medicinal

substances and auxiliaries are added without previously introduced into the slurry. The granules have good flowability and compressibility, so the tablets produced from such granules have high strength and compacted at low pressures.

If the densities of granules and the drug there is a significant difference, then maybe bundle compressed weights. As a result, the slurry is also possible over drying for delaminate upper tablet (capping) during pressing.

Granulation under fluidization. Granulation tableting mixtures in order to prepare them for tabulating in recent years in domestic and foreign pharmaceutical industry has found wide application method fluidization. Its main feature is that the material being processed, and then the resulting granules are continuously in motion. Basic processes of - mixing the components, moisturizing adhesive substance mixture solution, granulation, drying and granulate substances entering powdering - occur in one apparatus. Fluidized bed granulation is carried out in two ways:

- spraying the solution containing the drug and the auxiliary substance in the fluid system;
- granulating the powdery materials using fluidization.

Applying the first method, the granules are formed by applying a solution or suspension of a granulating surface initially introduced into a colony nuclei (nucleus may be a drug substance or indifferent material, e.g., sugar). In general, this method is a spray granulating solution fluidized system of initially introduced into a colony of nuclei, which are artificial "embryos" of future granules.

Another method of preparing granules - direct granulation of powders in a fluidized bed. To implement this method, the apparatus, the upper part of which is the process of granulation, while the bottom - the drying and processing of the granules (e.g., the device SMC). Currently used in the production of devices SG-30, SG- 60. The granules obtained in the fluidized bed, characterized by high strength and better flowability, which is a consequence of the regular

geometrical form of granules approaching spherical. This produces soft and porous agglomerates than the production of granules by wet granulation, which formed large agglomerates to be followed by grinding.

Formation and growth of the granules in the fluidized bed is due to two physical processes: caking and sticking when wetted with subsequent agglomeration. Pellet quality and fractional composition depend on many factors that affect the process, the main ones being the speed of the fluidizing gas composition and flow rate of granulating fluid, the temperature in the layer.

Granulation of compressing mixtures in a fluidized bed mixing is the first process step, affecting the quality of the granules. Uniformity of mixing is dependent on the operating mode of the aerodynamic system, the mixing ratio, shape, and particle density. For the improvement of the homogeneity of the compressed mass the fluidization conditions occurred by shaking.

When particles are mixing they are close to each other in shape and having a weight ratio of not more than 1:10, the mixing substantially occurs without separation at higher mixing ratios of the character depends on the shape and density of particles and aerodynamic parameters of the process and requires specific study in order to select the optimum mode.

When adding the granulating fluid to the particles occurs due to the granulation mass forces gluing both the liquid and the solution formed upon wetting of the liquid surface layer material being treated. In the drying process, into solid lumps, agglomerates partly disintegrate by friction between themselves and with the walls of the apparatus.

The process of granulation in a fluidized bed appears with simultaneous drying granules come with hot air. Drying the finished granulate is actually more to the desired residual moisture values. If, after termination of granulation compressing mixture is necessary for pressing residual humidity, additional drying is required.

Powdering the dried granulate produced in the same apparatus by adding to the granules antifriction agents and secondary mixing fluidity layer. The

granules obtained in the fluidized bed have number of advantages over the granules obtained by granulating a mechanical humidified: more rounded form of granules, better flowability and the fractional composition of a more balanced.

3. Standardization process of tablets

One of the basic conditions of industrial production of tablets is that the finished product with the requirements of regulatory and technical documentations. Quality of the tablets is determined by various indicators, which are divided into the following groups:

1. Organoleptic;
2. Physical;
3. Chemical;
4. Bacteriological;
5. Biological.

Definition of quality tablets begins with an assessment of their appearance (organoleptic properties), which are influenced by the following factors:

1. Compression conditions;
2. The adhesive and cohesive properties of the compressing mass, its moisture content;
3. Particle size distribution;
4. Surface and precision press tool;

The physical quality parameters include geometry (shape of the tablet, the geometric form of the surface, the ratio of the thickness to the diameter of the tablet, etc.) and its own physical characteristics (tablet weight deviations from the desired values of mass, strength values, porosity, bulk density, and figures appearance – coloring, spotting, integrity, availability of signs or inscriptions, no metallic inclusions, etc.).

The chemical indicators include: disintegration, solubility and constant chemical composition, the activity of the drug substance, the shelf life of tablets, their storage stability, etc.

By bacteriological quality pills are seeding microorganisms and bacteria
res of non-pathogenic nature of the content is not more than the number.

Quality control is carried out according to the finished tablets,
Pharmacopoeia requirements article "tablets", as well as private pharmacopoeia
articles on the following parameters:

Organoleptic properties - GPh XI ed., vol. 2, p. 154-155;

Mechanical strength - GPh XI ed., vol. 2, p. 157-158;

Disintegration - GPh XI ed., vol. 2, p. 158-159;

Dissolution - GPh XI ed., vol. 2, p. 159-160;

Average weight of the tablets and the deviation in the mass of individual
tablets - GPh XI ed., vol. 2, p. 156;

Drug content in tablets - GPh XI ed., vol. 2, p. 156;

Content uniformity - GPh XI ed., vol. 2, p. 156-157;

Evaluation of the external appearance of the tablets. 20 tablets are observed
visually.

Recess (wells, spilled parts tablets);

Dirt or dust on the tablets;

Marbling (uneven color, local, local color change);

Chipped (delaminating or chipped tablets, reduction in thickness);

Coalescence (two tablets sticking together or compound fracture of the
face);

Crumbling;

Deformation (violation roundness form);

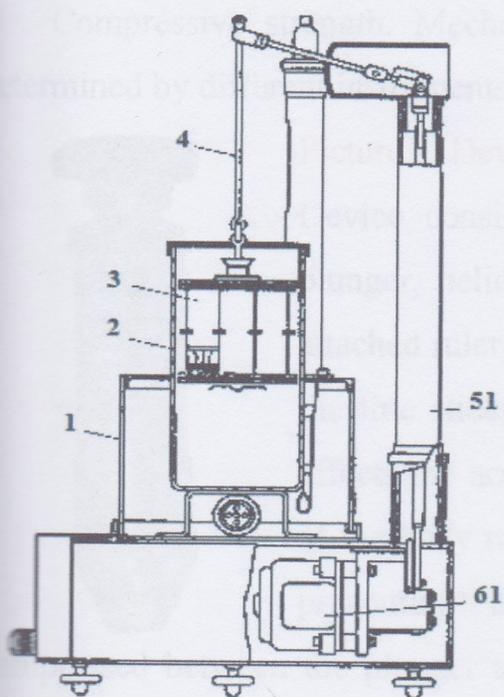
Scratches (causing risks - scratches on the surface of the tablets);

Tablets should be circular or other shape with flat or biconvex surfaces,
integral edges; the surface should be smooth and uniform, color – light green, if
private papers indicated otherwise. Determination of tablets' disintegration
is difficult. The most appropriate way to determine the disintegration of tablets would
be the observation of their behavior in the human stomach by getting X-ray
images. However, mass production of tablets is difficult, whereby the worldwide

accepted conventional methods for determining the disintegration of tablets, conducted in vitro, human. According to GPh XI to determine the tablet disintegration method is used and the device proposed by American scientists and Gershberg Stoll. Device AK- 545- 1 of the "Swinging basket" to determine the disintegration time of tablets, pills, granules and capsules produced Mariupol technological equipment medical industry. The device consists of a swinging baskets (3) of the vessel (2) with a liquid medium (water, artificial gastric or intestinal juice), which is immersed in a thermostatic device basket (1), which allows to maintain a constant temperature of the medium within $37 \pm 2^\circ \text{C}$ and an electric motor (6) informing the basket reciprocates. Swinging basket consists of 2 Bakelite discs with a diameter of 90 mm with 6 holes concentrically located. In hole disc inserted glass tube length of 77.5 mm and an outer diameter of 25.5 mm. The lower disk is provided with a mesh of stainless steel wire with 2 mm diameter holes. Basket by a steel rod (4) attached to the lever (5) of the electric motor (Pict. 1).

The advantage of this method is the standardization of the test conditions, the constant amplitude of oscillation frequency of 28-32 cycles per min., particle removal disintegrated tablets, constant temperature, regulation of the particle size, the ability to check 5-6 tablets at the same time, mechanization definition.

Picture 1. Disintegration tester.



The disadvantage is the need for visual observation to determine the moment of the final disintegration of tablets. A more refined method is to define the tablet disintegration in the device by "Erweka" (Germany). This device differs by producing automatic termination fluctuations baskets in a moment of complete disintegration of the tablet. Simultaneously automatically stop the

and time fixed disintegration.

ns disintegrating tablets:

onventional tablets - 15 min;

oated tablets, soluble in the stomach - not more than 30 minutes. Tablets
ed with the enteric coating should not dissolve in 1 hour in a solution of
ochloric acid 0.1 mol/l, and after washing with water should decay by no
e than 1 hour in an alkaline solution of sodium hydrocarbonate;

ublingual tablets - water, 30 min;

tablets for the preparation of solutions - water, 5 min;

Sustained-release tablets - according to procedures described in the
macopoeia of individual articles;

Determination of the mechanical strength of tablets. Determination of the
hanical strength of tablets performed on instruments, some of which allow
o determine the compressive strength (split), others - to abrasion. Objective
ssment of the mechanical properties of the tablets can be obtained by
ducting the determination of their strength in both ways. This is explained by
fact that a number of oral agents, meeting the requirements for compression
easily edge and for this reason are substandard. It should be noted that the
ermination of the compressive strength is not pharmacopoeia method.

Compressive strength. Mechanical strength tablets compression can be
etermined by different instruments.

Picture 2. Device to determine the strength of tablets

Device consists of a cylindrical housing in which the
plunger, helical springs, pressure screw and nut. To nut
attached ruler with scale graduated in kilograms. Placed on
the line slider that is used to lock the testimony, which
affects the arrow associated with the plunger. In the wall
of the body make a slit, which includes nuts and plunger,
preventing them from turning. The test tablet is

mpressed between the plunger and the stop fixed on the housing. Screw is



rotated by a handwheel. The scale is graduated at 15 kg. Tablet placed edgewise, compressed to destruction. The slider on the ruler captures dynamometer load that caused the destruction of the tablet. It is necessary to determine the resistance of at least 3 tablets and calculate the arithmetic average of these measurements (Pict. 2).

Index of the strength of tablets is calculated by the formula:

$$K = \frac{P}{d * h}$$

where K - component strength, MPa;

P - breaking load, H;

d - diameter of the tablet at the middle, mm;

h - the height of the tablet in the center, mm.

Strength index should be 0,45-1,2 MPa.

The device model TVT firm " Erweka " the load is transferred to the tablet lever-weight method, minimal measurement error. The device operates semi-automatically. The test tablet placed in a special box on the anvil, height-adjustable, and is applied to the cone-shaped piston, which puts pressure on the tablet before its destruction. The amount of pressure that caused the destruction of the tablet device is fixed to a graduated scale from 0 to 15 kg. Mechanical strength of tablets is calculated by the formula:

$$q_m = \frac{P_r}{K_f * h * d}$$

where q_m - mechanical strength of the tablets on the radial compression, MPa;

P_r - destructive force, H;

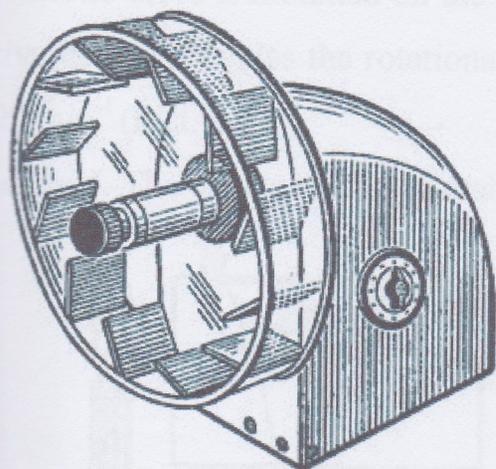
K_f - form factor;

h - the height of the tablet, mm;

d - diameter of the tablets, mm.

Abrasion resistance. Mechanical strength is characterized by the degree of abrasion of tablets. Abradability observed when packing, packaging and transport, being particularly strong on the filling machines. Education is a sign

of abrasion powder dust on the tablets and packaging. Abradability determined in a drum type – friabilator 545-P-AA-8 (Pict. 3)



Pict.3. Friabilator type 545- P-AA-8

The apparatus consists of a 200 mm diameter drum with a removable lid, the inner perimeter 12 of the blades which are arranged at an angle of 20° to the tangent of the drum, and the electrical mechanism for rotating the drum at a speed of 20 turn/min. 10 tablets, dust-free and weighed to the nearest 0.001 g

placed in a drum, screw the lid and include the device for 5 minutes, which corresponds to 100 revolutions of the drum. When the time de-dusting the tablets and determine their weight up to 0,001 g abrasion strength tablets percentage calculated by the formula:

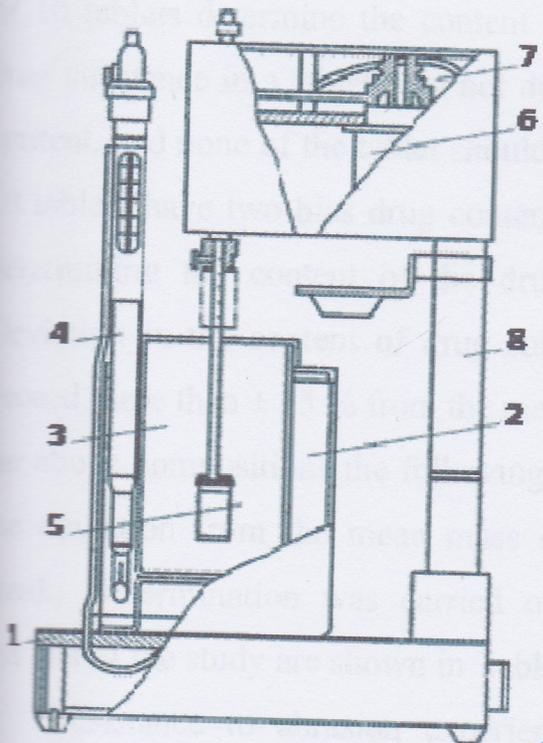
$$\Pi = 100 - \frac{P_{start} - P_{finish}}{P_{start}} \times 100$$

where R_{start} , R_{finish} - weight of the tablets before and after abrasion, respectively; form tablets should not be changed in the process of rubbing. Abrasion resistance should be less than 97 %. For the coated tablets, and abrasion resistance triturationsnyhtabletok not determined.

Dissolution. Determination of tablet disintegration gives no information on the release of drug from the dosage form and disintegrated does not allow us to conclude that they are available. The more reliable method of controlling is the "dissolution test". When this amount of the drug is analyzed (at intervals), from the diffusing whole or broken tablets into the dissolution liquid (water, 0.1N hydrochloric acid solution, 0.1 N sodium hydroxide solution, buffers, artificial digestive juices, etc.). The device is arranged and operates as follows: on the basis of (1) installed thermostatted vessel (2) into which the glass (3) for a medium - solvent. Required temperature (37 ± 1 ° C) provided by a contact

thermometer (4). Inside cup is introduced mesh basket (5) with the test drug. Rotation baskets carried by an electric motor (6) through step pulleys (7) belt drive. The drive is mounted on the column (8), standing on the basis of (1). The drive device provides the rotational speed of baskets within the 50, 100, 150 and 200 min⁻¹ (Pict. 4).

Picture 4. The device design "Rotating basket" type AK- 545- 7



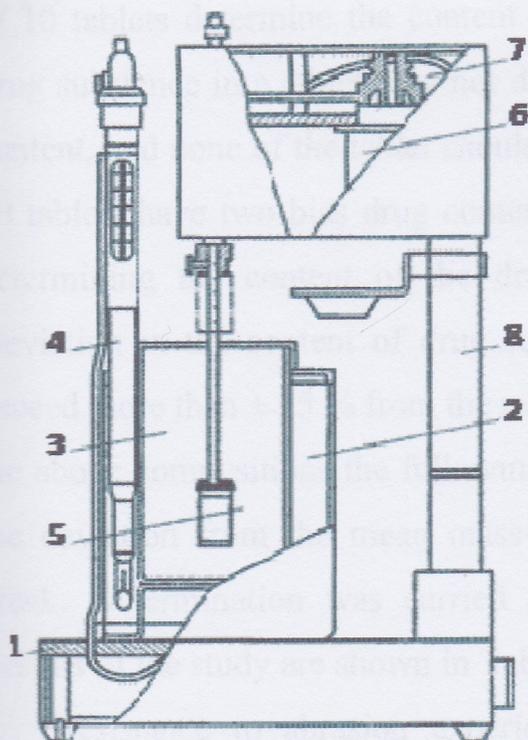
To operate the instrument in a thermostat filled with 2 dm³ of water in a beaker and 1 dm³ of liquid medium (purified water, simulated gastric or intestinal juice). Basket on medium lowered the glass so that the distance to the bottom of a glass was 20 ± 2 mm. The dissolution rates of the active substance from the tablets or capsules are calculated as the average of six, and in some cases from 12 determinations.

Average weight and variations from the weight. Weigh 20 tablets to the nearest 0.001 g, and the result is divided by 20. Separated tablet mass is determined by weighing 20 tablets individually to the nearest 0,001 g, the deviation in the mass of individual tablets (except coated tablets by extension) is allowed within the following limits:

- tablet weighing 0.1 g and less than ± 10 %;
- weight of 0.1 g and 0.3 g of less than ± 7,5%;
- mass and 0.3 ± 5 %;
- the weights of individual coated tablets obtained by building shall not differ from the average weight by more than ± 15%. Only two tablets may be deviations from an average weight in excess of these limits, but no more than twice. Determination of drug tablets. Take a sample of mashed tablets (not less than 20 pieces), for tablets, coated tablets, tests are carried out a certain number

thermometer (4). Inside cup is introduced mesh basket (5) with the test drug. Rotation baskets carried by an electric motor (6) through step pulleys (7) belt drive. The drive is mounted on the column (8), standing on the basis of (1). The drive device provides the rotational speed of baskets within the 50, 100, 150 and 200 min⁻¹ (Pict. 4).

Picture 4. The device design "Rotating basket" type AK- 545- 7



To operate the instrument in a thermostat filled with 2 dm³ of water in a beaker and 1 dm³ of liquid medium (purified water, simulated gastric or intestinal juice). Basket on medium lowered the glass so that the distance to the bottom of a glass was 20 ± 2 mm. The dissolution rates of the active substance from the tablets or capsules are calculated as the average of six, and in some cases from 12 determinations.

Average weight and variations from the weight. Weigh 20 tablets to the nearest 0.001 g, and the result is divided by 20. Separated tablet mass is determined by weighing 20 tablets individually to the nearest 0,001 g, the deviation in the mass of individual tablets (except coated tablets by extension) is allowed within the following limits:

- tablet weighing 0.1 g and less than ± 10 %;
- weight of 0.1 g and 0.3 g of less than ± 7,5%;
- mass and 0.3 ± 5 %;
- the weights of individual coated tablets obtained by building shall not differ from the average weight by more than ± 15%. Only two tablets may be deviations from an average weight in excess of these limits, but no more than twice. Determination of drug tablets. Take a sample of mashed tablets (not less than 20 pieces), for tablets, coated tablets, tests are carried out a certain number

of tablets of the private papers. Variations in the content of drugs should be at a dosage of drugs to $0.001 \text{ g} \pm 15\%$; from $0,001$ to $0,01 \pm 10 \%$; from $0,01$ to $0,1 \pm 7,5\%$; 0.1 and over $2 \pm 5 \%$, unless otherwise specified in the monograph.

Test uniformity of dosage. Held for uncoated tablets with a content of less than 0.05 g and the drug substance and the tablets sheath with drug content of 0.01 g or less. From the series to be tested, sampled in an amount of 30 tablets. In each of 10 tablets determine the content of the drug substance. The content of the drug substance in a tablet may not deviate by more than $\pm 15 \%$ of the average content, and none of the tablet should not exceed $\pm 25 \%$. If the tested tablets of 10 tablets have two bias drug content by more than $\pm 15 \%$ from the average, determining the content of the drug in each of the remaining 20 tablets. Deviation in the content of drug substance in any of the tabs 20 should not exceed more than $\pm 15 \%$ from the mean. All of the tablets obtained according to the above compositions the following parameters were determined: appearance, the deviation from the mean mass disintegration, resistance to abrasion and break. Determination was carried out according to the procedures GF XI. Results of the study are shown in Table 3.7.

Resistance to abrasion experienced almost all tablets "Pyrnicam", the discrepancy GPh XI edition requirements. Deviations from the average weight of all of the analyzed compounds were within acceptable limits and do not exceed 5%.

The masses obtained for formulations, in the process of granulation were unsatisfied, that was the reason for getting low-quality pellets.

Thus, as the above parameters were chosen optimal composition 1 composition, in which as the binder used was saturated solution of polyvinylpyrrolidone. The technology of obtaining the recommended prescription tablets by wet granulation is as follows: calculated amount of ingredients, auxiliary substances - pulverized and sieved through a sieve with a hole diameter of 150 microns humidified with binder, passed through a sieve with a hole diameter of 1000 microns and $40-50^\circ\text{C}$ dried at a temperature up to

optimal residual moisture. Then finished granules dusted with calcium stearate. After studying the technological properties of the resulting mass is pressed into tablets having an average mass of 0.55 g in a matrix of 12 mm in diameter at a pressure of 50 N. In the following quality indicators obtained pellets were examined in accordance with the requirements of the GPh XI, as well as other conventional methods. Assessment of quality was carried out on the following parameters: appearance, geometric shape, line height to diameter, average weight, quantitative content of active substances, disintegration and dissolution, abrasion resistance and fracture.

From the presented data it follows that the tablet obtained by wet granulation prescriptions 3 meet the requirements in terms of GPh XI appearance, average weight and the deviation from the mean mass, fracture strength and abrasion resistance. The tablets obtained by the 1, 2 and other prescriptions are characterized by great time disintegration, which averaged more than 17 minutes. The tablets obtained by the 4 prescriptions have a disintegration time of at least 15 minutes, which is a risk in the transition to the working environment. The best indicators of the disintegration time and other indicators observed prepared tablets for 3 (3.55 and 5.00 minutes, respectively).

However, the quality of the tablets depends on pressing pressure, which affects tablets disintegration time and strength. In the connection with "Pyronicam" that we carried out a study of pressing conditions on the quality of the tablets. Peculiar to decompose in a particular environment for a specified time, it is one of the main characteristics of the tablets. This tablet properties, mainly depends on the physical and technological characteristics of the material to be tableted and conditions of pressing. Therefore, in a special series of studies devoted to the study of the influence of environment and compression mode

In the experiments different diameter molds (10, 11, 12mm) were used. In the experimental studies have established that all the tablets obtained on all 5 prescriptions optimal molds were 10 mm. Tablets specific weight of 0.50 g a

meter of 10 mm were pressed on a hydraulic press at pressures of 50-200 Pa.

The results of the qualitative indicators of the recommended tablets "Pyrnicam" showed the following: the appearance of the tablet-green or light green colored, odorless, cylindrical form, with valium, breaking strength ranged from 35.8 to 40 N, the ratio tablet height to diameter of 35-37%, abrasion resistance of 99.85%, disintegration time is about 4 minutes. Strength activity of tablets plays an important role in maintaining their integrity during packaging, transport and storage. It also depends on the amount and nature of binders, and the magnitude of the pressing pressure of the materials humidity. Also, one of the main characteristics of the tablets is the ability to disintegrate and dissolve in water for a time not exceeding the regulated, all of normative – technical documentation as this is proved therapeutic effect on the body. Disintegration of tablets mainly depends on the physical and technological characteristics of the material to be compressed: compacting pressure imposed amount of lubricants and binders, the method of manufacturing tablets, etc.

The results of the dependence of the quality of tablets "Pyrnicam" by changing the pressure showed that quality tablets obtained in the application of compaction pressure 100-180 MPa. With an increase in compaction pressure the disintegration time also increases, resistance to crushing increases and increases abrasion. From these data, it is evident that the tablets "Pyrnicam" with satisfactory characteristics can be obtained when using a compacting pressure in the range 100-180 MPa. By increasing the pressure to 200 MPa significantly increased disintegration time and resistance to crushing.

Thus, the comprehensive research on technology based on indicators of physical, chemical and technological properties of the optimal composition "Pyrnicam" tablets. The results are shown on the table 14.

Table 14. Standardization results of "Pyrnicam" tablets

Studied rates	Results				
	1 series	2 series	3 series	4 series	5 series
Appearance	Light green colored, specific odored, cylindrical tablets				
Proportion of height to the diameter of tablets, %	35.02	35.70	34.90	35.09	35.55
Average mass and exception from it , %	0,512±2.4	0,498±0.4	0,520±4%	0,508±1.6	0,485±3
Strength to break, N	56.34	58.35	57.87	56.53	57.36
Friability strength, %	97.36	98,99	98,97	98,37	99,85
Disintegration, min	3.95	3.89	3,49	4.02	4.25

Conclusions for the 3rd chapter. The suitable excipients are chosen for tablet form:

Pyriminamide – 0.25

Calcium carbonate – 0.1

Calcium hydroxide – 0.126

Hydrochloric acid – 0.017

Starch – 0.002

Calcium stearate – 0.005

Tablets are made with method of wet granulation. The process is shown as algorithm. The results of the qualitative indicators of the recommended tablets "Pyriminamide" showed the following: the appearance of the tablet-green or light green colored, odorless, cylindrical form, with valium, breaking strength ranged from 35.8 to 40 N, the ratio tablet height to diameter of 35-37%, abrasion resistance of 99.85%, disintegration time is about 4 minutes.

Two experiments further research in a clinical setting.

The objective of this phase of the work was to determine the rate of release of the substances from tablets "Pyriminamide" by *in vitro*.

The main method of study in the biopharmaceutical properties of drugs by *in vitro* method, this method is related to the apparatus "Rotating basket" and is included in GPh XI. Therefore, to determine the rate of release of active substance from tablets "Pyriminamide" study was performed using this method.

It should be noted that the release rate of the active substances have various factors used: volume and pH of the dissolution medium, the speed of rotation of the basket.

For the selection of the optimal pH of the dissolution medium were used different medium with different pH values. As neutral condition – purified water, acidic – 0.1 N hydrochloric acid and alkaline – 0.1 N sodium hydroxide solution. The volume of the dissolution medium volume – 1000 ml. This volume has been selected, considering the sensitivity of the method developed by the identification of active substances in tablets "Pyriminamide" (Fig.14).

CHAPTER IV. STUDYING THE BIOLOGICAL EFFECTIVENESS AND SHELF LIFE OF TABLETS

1. Research of biological efficacy of tablets with the method of in vitro

Biopharmacy - section of Pharmacy, to study the impact of physical and chemical properties, the characteristics of the dosage form and drug preparation technology on the biological effects of medicinal matters. Biopharmacy examines the influence of pharmaceutical factors on the therapeutic efficacy of drugs. The bioavailability of drugs is determined by the amount of drug reached the systemic circulation. A prerequisite to the emergence of Biopharmaceutics as a science were numerous facts of therapeutic non-equivalence of the same dose of the drug. The biological equivalence of drugs is to compare the bioavailability of drugs synonymous. Study the bioavailability of drugs, medications or dosage forms usually starts with in vitro tests, and ends with the in vivo experiments further research in a clinical setting.

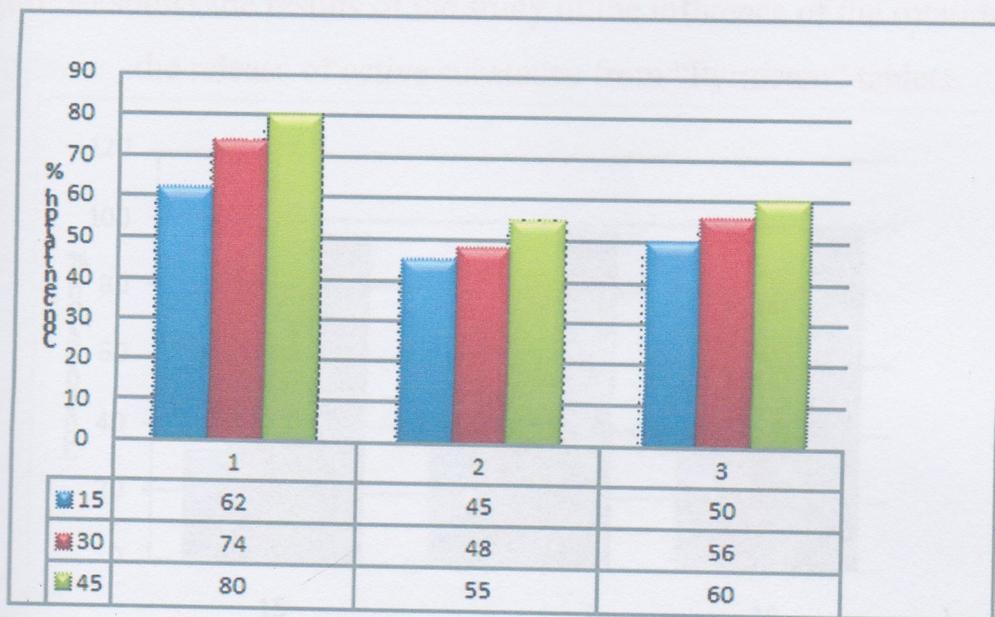
The objective of this phase of the work was to determine the rate of release of active substances from tablets "Pyrnicam" by in vitro.

The main method of study in the biopharmaceutical properties of drugs by in vitro method, this method is related to the apparatus "Rotating basket" and included in GPh XI. Therefore, to determine the rate of release of active ingredient from tablets "Pyrnicam" study was performed using this method.

It should be noted that the release rate of the active substances have various factors used adjuvants, volume and pH of the dissolution medium, the speed of the basket.

For the selection of the optimal pH of the dissolution medium were used solvent medium with different pH values. As neutral condition - purified water, acid - 0.1 n hydrochloric acid and alkaline - of 0.1n sodium hydroxide solution. In experiments was dissolving medium volume - 1000 ml. This volume has been selected, considering the sensitivity of the method developed by us quantification of active substances in tablets "Pyrnicam" (Fig.14).

Figure 14 shows the results of studying the influence of pH of the dissolution medium on the dissolution rate of the tablets "Pyrnicam".



1-alkaline medium(0.1 n NaOH solution)

2-acidic medium (0.1n HCl solution)

3-neutral medium (purified water)

Based on the results of the study "Pyrnicam" effect of pH on the dissolution rate of the tablets for further research we recommend the use of a alkaline environment. In experiments in developing test "Dissolution" is a study to determine the optimal speed of rotation of the baskets was performed at 50, 100, 150 and 200 rot/min. It is clear from these results that the release of active substances from the "Pyrnicam" tablets in various baskets speeds occurs rapidly.

1-Rotation speed of the baskets 50 rot/min

2-Baskets' rotation speed of 100 rot/min

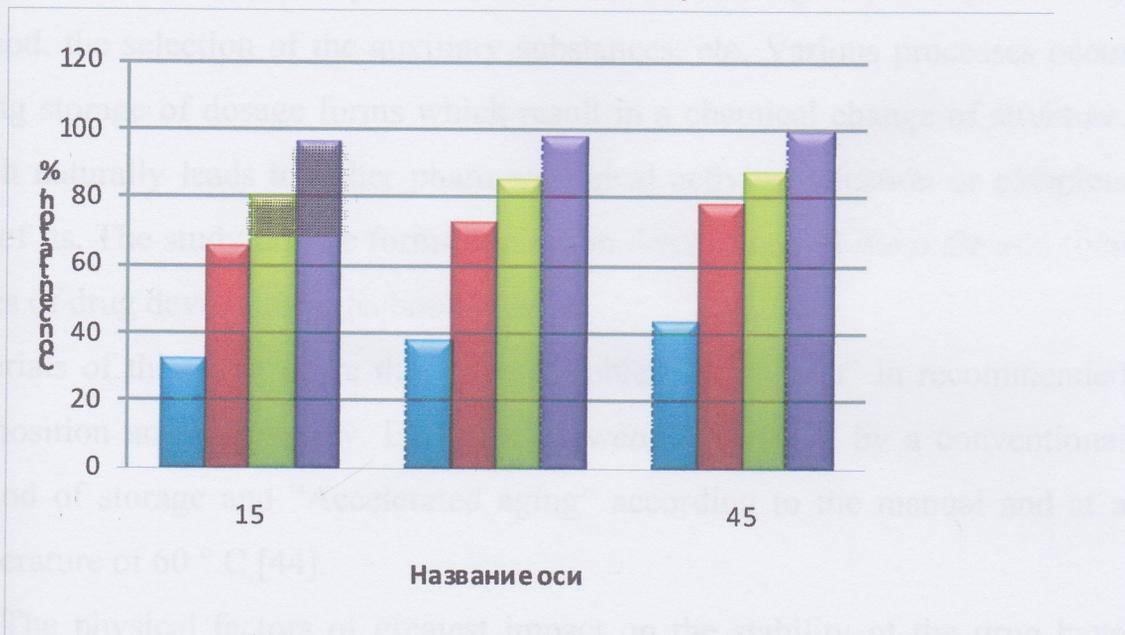
3-Baskets' rotation speed of 150 rot/min

4-Baskets' rotation speed of 200 rot/min

It should be noted that the basket at a rotational speed of 100 rev/min the concentration of active substances passed into the solution for 45 minutes is over 50%, which meets the requirements of the GPh XI. From the above, for further

analysis of the finished products with the biopharmaceutical viewpoint commended basket rotation speed of 100 rot/min (Fig.15).

Figure 15 shows the results of the study of the influence of the rotation speed to the release of active substance from "Pyrnicam" tablets



Rotation speed of the baskets 50 rot/min

Baskets' rotation speed of 100 rot/min

Baskets' rotation speed of 150 rot/min

Baskets' rotation speed of 200 rot/min

2. Studying the shelf life of tablets with the method of accelerated ageing

The stability (resistance) of drugs and its quality are closely linked. Drug stability study funds, depending on various factors, establishing expiration dates of drugs - one of the most important issues dealt with by specialists from various areas of pharmacy. Under the influence of external factors may occur in medicaments change their physical properties, chemical composition, which in turn affects their stability and therapeutic efficacy. One of the major challenges of modern pharmaceutical technology is to develop a convenient dosage forms for the application, stable during storage.

Based on the above, further studies examined the effect of various conditions on the stability of the tablets "Pyrnicam" we received the recommended composition and technology, and determined their expiration

dates. Experiments were carried out by a conventional method of storage and "Accelerated aging" according to the manual and at 60 ° C.

The stability of formulations greatly influences the physical state of a substance, the storage temperature, the ambient air, light, packing, cooking method, the selection of the auxiliary substances, etc. Various processes occur during storage of dosage forms which result in a chemical change of structure, which naturally leads to either pharmacological activity reduction or complete loss of its. The study dosage forms expiration dates is one of the main and final stages of drug development technologies.

Materials of this study were the obtained tablets "Pyrnicam" in recommended composition and technology. Experiments were carried out by a conventional method of storage and "Accelerated aging" according to the manual and at a temperature of 60 ° C [44].

The physical factors of greatest impact on the stability of the drug have temperature, light and humidity. The first stage of the research was to study the physical and chemical, qualitative and quantitative indicators of the original tablet samples. In this case quality indicators were assessed such as appearance, average weight and deviation from average weight, solubility, disintegration, stability, moisture, microbial purity, quantitative content of active ingredient.

of these figures were determined according to the GPh XI. In the next stage of the experiment tablets packaged in the following permitted for use in medicine are 4 types of packaging: clear glass jars (TC-64-228-84) with plastic screw caps and seal (TC-64-2-250-75); amber glass jars (ST 64-2-71-8) with plastic screw caps and seal (TC 64-2-250-75) contour - uncelled polyethylene packaging made of laminated paper on TC 13-7308001-477-85, contour-package of PVC film marks the VC-73 (Tab. 17 in the abstract).

The stability of the drugs depends on the chemical composition and properties of the packaging material. In the study of the possibility of the use of packaging material requires the prior conduct of the physical, chemical and biological testing. Particularly high requirements for packaging materials

intended for the storage of medicines as well as storage day depends on the temperature (Tab15).

Important is not only the stability of the packaging material, but also its ability to protect the drugs from the effects of temperature, light and humidity. Therefore, after the packaging material stability study investigated the stability of samples of drugs or dosage forms placed in the same package. Based on this let expiration dates of medicines in respective package (Tab.16).

Table 15. The linking of storage days on the temperature

$(t_1 - t_{pr})$ °C	10	20	30	40	50	60	70
The steps of quality rate assessment	92 days	46 days	23 days	11,5 days	6 days	69 hours	34 hours

Packed into different types of packaging tablet "Pyrnicam" after the experiment meet the requirements set for a tablet formulation. For example, the appearance of the tablets did not change over the entire period of the study, the variation from the average weight of up to 3.95%, disintegration ranged from 3-4 minutes, the abrasion resistance of 98.5 -99.5%, breaking strength 40-45 N and quantitative content of active ingredient is in the range 98,7-99,2% (Tab. 18 the abstract).

Table 16. The calculations of shelf-life longevity

Durability	Experimental shelf-life longevity, in days						
	$(t_1 - t_{pr})$, °C						
	10	20	30	40	50	60	70
2 years	365	182	91	46	23	11,4	5,7
3 years	548	274	137	68	34	17	8,6
4 years	730	365	182	91	46	23	11,4
5 years	913	456	228	114	57	29	14,3

Thus, we recommended the composition and technology of production tablets, as well as the types of packaging used tablets provide stability for 3 years in the research method of "Accelerated aging", when stored under natural standard conditions for 1,5 years.

Conclusion to the 4th chapter. Researched the bioefficacy and shelf life of tablets. For the selection of the optimal pH of the dissolution medium were used solvent medium with different pH values. As neutral condition - purified water, acid - 0.1 n hydrochloric acid and alkaline - of 0.1n sodium hydroxide solution. In experiments was dissolving medium volume - 1000 ml. Based on the results of the study "Pyrimicam" effect of pH on the dissolution rate of the tablets for further research we recommend the use of a alkaline condition. Tablets are packaged into 4 types of packaging materials. All packages were suitable for wrapping. For example, the appearance of the tablets did not change over the entire period of the study, the deviation from the average weight of up to 3.95%, disintegration ranged from 3 to 4 minutes, the abrasion resistance of 98.5 - 99.5%, breaking strength 40-45 N and quantitative content of active ingredient is in the range 98,7-99,2%.

CONCLUDING CLAUSES

The world pharmaceutical market was observed and consequently it was found that this sector has taken the second place in the global economy. For example, in countries such as Japan, USA, France, Switzerland, Belgium, and many others, the annual drug consumption per capita numbered to \$ 250. In a large number of countries like Sweden, Canada, Finland, Denmark, the Netherlands, UK, Spain, Portugal, Argentina, Greece, Ireland it varies in the range of 250 dollars. In Czech Republic, Hungary, Poland, Russia, Bulgaria the expenditure of medicines does not exceed \$ 50-100. Also in our country the pharmaceutical industry is blooming. Nowadays, there are 154 appropriate licensed ventures engaged in production of drug facilities and medical items in Pakistan. Leaders of the last 2 years in the development and introduction of new products are "Novopharma Plus", "Nika Pharm", "DentaFill Plus", "Nobel Farmsanoat" and "Remedy Group", and it should be noted that 22 members of "Uzfarm sanoat" SJS have the international quality certificate of ISO: "Novopharma Plus", "Nika Pharm", "Radiks", "Jurabek Laboratories", "DentaFill Plus", "Zamona Rano", "NASA", "Remedy", "Remedy group", "Germed Pharm", "Samsun-Tashkent-Pharm", "Gufik-Avicenna", "Asia Med", "Reka-Med Farm", "SAMO", "Elastikum", "MerryMed Farm", "Nobel Farmsanoat", "Galenika", "Makrofarm-Optima", "Immunomed" and "Armed". Most of these enterprisers engaged in tablet manufacturing. In addition, some of them specialized in manufacturing original drugs contain with complex matters of 3d metals.

This complex matter is light green colored fine crystalline powder, without a specific smell and taste. The crystal is rod shaped and size is between 8-20 nm. IR-spectrum, UV-spectrum of this complex is identified, as well as the composition temperature of matter is studied by the method of TGDSC. The absorption of complex gives the absorption at 289 nm, whereas the decomposition temperature numbers to 228.7. The pH of the complex is between 5.3 and 6.5. The method of HPLC was chosen as a quantity identification method of

complex. *Technological properties of powder-like medicinal substances include fractional (granulometric size) composition, apparent (bulk) density, relative density, porosity, compression coefficient, flowability (fluidity), compressibility, the strength of tablet ejection from the matrix, moisture content, dispersion and others were determined. Certain pharmacological studies carried out in the central vivarium of Tashkent pharmaceutical institute. The effect of the drug on hematopoiesis was studied by determining the number of reticulocytes in peripheral blood. It was established that the drug administered orally at a dose of 15 and 25 mg/kg increased the amount reticulocytes to 155-171% in the peripheral blood. The effect of the drug on diabetes was carried on in the experimental conditions on rats weighing 160-187 g of both sexes. It was found that the drug showed a significant hypoglycemic effect - at a dose of 25 mg/kg in 60 minutes the drug reduced the blood sugar levels by 32.1%. The microbiological purity and activity were studied and results showed that substance has different microbial activities.*

The suitable excipients are chosen for tablet drug form:

Pyronicam – 0.25

Calcium carbonate – 0.1

Sodium hydrocarbonate – 0.126

Citric acid – 0.017

PVP – 0.002

Calcium stearate – 0.005

Tablets are made with method of wet granulation. The process is shown as an algorithm. The results of the qualitative indicators of the recommended tablets “Pyronicam” showed the following: the appearance of the tablet-green or light green colored, odorless, cylindrical form, with valium, breaking strength ranged from 35.8 to 40 N, the ratio tablet height to diameter of 35-37%, abrasion resistance of 99.85%, disintegration time is about 4 minutes.

Researched the bioefficacy and shelf life of tablets. For the selection of the optimal pH of the dissolution medium were used solvent medium with different

pH values. As neutral condition - purified water, acid - 0.1 n hydrochloric acid and alkaline - of 0.1n sodium hydroxide solution. In experiments was dissolving medium volume - 1000 ml. Based on the results of the study "Pyrnicam" effect of pH on the dissolution rate of the tablets for further research we recommend the use of a alkaline condition. Tablets are packaged into 4 types of packaging materials. All packages were suitable for wrapping. For example, the appearance of the tablets did not change over the entire period of the study, the deviation from the average weight of up to 3.95%, disintegration ranged from 3 to 4 minutes, the abrasion resistance of 98.5 -99.5%, breaking strength 40-45 N and quantitative content of active ingredient is in the range 98,7-99,2%.

Bibliography list

Normative documents:

1. The Cabinet of Ministers Resolution from 05.08.2000, № 207 "On additional measures to support the internal market with medicines and medical items".
2. The Cabinet of Ministers Resolution from 14.08.1996, № 283 "On measures of state support of the medical and pharmaceutical industry in the Republic of Uzbekistan".
3. The Law of the Republic of Uzbekistan "On Advertising" (from December 25, 1998, number 724-I).
4. The Law of the Republic of Uzbekistan from 25.04.1997 № 415-I «On medicines and pharmaceutical activity".
5. The Law of the Republic of Uzbekistan "On metrology" from 28.12.1993 № 1004-XI.
6. The Law of the Republic of Uzbekistan "On certification of products and services" 28.12.1993 № 1006-XII26.
7. The Resolution of the Cabinet of Ministers from 13.05.2010 № 91 "On measures of further improvement of the licensing order of pharmaceutical activity".
8. The Presidential Decree of the Republic of Uzbekistan from June 2, 1993, № PD-609 "On the Formation of the Uzbek State Joint-Stock Concern pharmaceutical industry ("Uzfarmprom)".
9. The Presidential Resolution of the Republic of Uzbekistan 04.02.2014 № PR-2120 "On the Program of localization of ready products, components and materials manufacturing in the 2014-2016".
10. The Presidential Resolution of the Republic of Uzbekistan from 15.12.2010 № PR-1442 "On the priorities of industrial development of Uzbekistan in 2011-2015".
11. The Presidential Resolution of the Republic of Uzbekistan from 07.07.2011 № PR-1590 "On measures for further deepening the localized

manufacturing of ready products, components and materials based on industrial cooperation for 2011-2013".

12. The Presidential Resolution of the Republic of Uzbekistan from 04.10.2011, № PR-1623 "On the Program of priority measures to increase production volumes and the development of new types of competitive products".

13. The Presidential Resolution of the Republic of Uzbekistan from 30.04.2013 № PR-1961 "On additional measures to increase the production and expansion of domestic consumer goods range".

14. The Presidential Resolution of the Republic of Uzbekistan of 19.11.2007 № PR-731 "On the program of modernization, technical and technological re-equipment of the pharmaceutical enterprises' branch for the period until 2011".

15. The Resolution of the Cabinet of Ministers from 06.08.1994 № 404 "On urgent measures to improve the supply and distribution of drugs and medical products in the country".

16. The Resolution of the Cabinet of Ministers from 13.05.2010 № 91 "On measures of further improvement of the licensing order of pharmaceutical activity".

17. The Resolution of the Cabinet of Ministers from 29.01.2009 № 26 "On additional measures to improve the competitiveness of domestic manufacturers".

18. The Resolution of the Cabinet of Ministers from 13.05.2010 № 91 "On measures of further improvement the order of pharmaceutical activity licensing".

19. The Resolution of the Cabinet of Ministers from 28.11.2012 № 333 "On additional measures to shorten the production costs and decrease the prime cost in the industry".

20. The Resolution of Cabinet of Ministers from 21.12.1999 № 538 "On measures to further expansion the range and the volume of production of medicines and medical products in the country".

21. The Resolution of the Cabinet of Ministers from 25.05.1995 № 181 "On state control of drugs quality, medical devices and products preventive nutrition".

The Presidential Decree of the Republic of Uzbekistan from 14.07.1994 PD-916 "On regulation of medicinal products in the country".

The Presidential Decree of the Republic of Uzbekistan from 08.11.1994 D-985 "On additional measures to saturate the domestic market with drugs medical items".

The Presidential Resolution of the Republic of Uzbekistan from 22.2011, № 49 "On the import regulation of ready pharmaceutical products".

Textbooks and manuscripts

Ajgikhin I.S. Technology of drug forms. -M.: Medicine. 1980.-p. 127.

Beregovich B.B., Sapojnikova E.A., Djalilov X.K. and others. Textbook. – Tashkent, 2011.

British Pharmacopoeia. Monographs: Medicinal and Pharmaceutical Substances.- London, 2007.r Vol.I,II.-3c.

Chueshov V.I. Industrial technology of drugs. Volume 2. Kharkov. 2002.

European Pharmacopoeia.-Sainte-Ruffin, 1997.-P.1487.

Federal guidance on managing the regulation of drug usage. Edition. XII. 2011. –p. 956.

Fedotov A.E. Basics of GMP. Drug manufacturing. –M.: Asinkom, 2012.

Gavrilov A.S. Pharmaceutical technology of drug preparation. – Tashkent: GEOTAR-Media, 2010.

Government pharmacopoeia of Byelorussian Republic. 2009. ISBN 985-6742-

Halmatov H.H., Tatar A.Z. Periodic system of elements and biological role. Tashkent: Medicine, 1985. – p. 77.

Krasnyuk. I.I., Mixaylova G.V. Pharmaceutical technology. – Tashkent: GEOTAR-Media, 2013.

Kudrin A.V., Gromova O.A., Trace elements in neurology. – M.:GEOTAR-Media, 2006. – p. 11-85.

Maksimina E.A., Minazova G.I., Chukreeva N.V. Standardization and quality guarantee of drugs. –M.:Medicine, 2008.

38. Menshutina N.V., Mishina Y.V., Alves S.V. Innovative technologies and apparatus of pharmaceutical manufacturing, vol.1.-M.:Binom, 2012.
39. Miralimov M.M. Technology of complex preparations. –Tashkent, 2001.
40. Nozdryuhina L.R., N.I. Grinkevich. Violation of microelement exchange and ways of its correction. - M.: Nauka, 1980. - p. 60.
41. “Pharm index-Practice” edition 2, 2001.-p. 41-71.
42. Salidra B.A., Malaya L.T.etc. Pharmacotherapy. - Kharkov. NUPh, 2000. - p. 152.
43. Skalny A.V., Rudakov I.A. Bioelements in medicine. - M.: ONYX XXI century - World - 2004 - p.8,139.
44. Temporal directions on carrying out the works on indentifying the durability of drugs with the method of “Accelerated aging” in high temperatures.- I-42-2-2.-M., 1983.
45. The Pharmacopoeia of Yapan.-Twelfth edition (English version).-Yapan, 1991.-P.258.
- The United States Pharmacopeia. The National Formulary. USP XXIV. Winbrook Parkway, Rockvill M.D., 2000.-P.546.
46. Tyukavkina N.A., Berlyand A.S., Elizarova T.E. and others. Standardization and quality control of drug items. _M.:Medical informative agency, 2008.
47. Vidal reference book. Medicinal drugs in Russia. 2014.
48. Zhavoronkov A.P., Risch A.A., Stochkova L.S. Microelementoses of person - M.: Medicine, 1991. – p. 305.

Auxiliary literature

49. Saydaliyeva A.K., Mixed liganded coordination compounds of 3d metals with vitamins B3, B5, B6 some of their isomers, derivatives and α -amino acids: Phd. of chemical sciences. – Tashkent, 2008. –p.5.
50. Shabilalov A.A. Coordination chemistry of biomedicine 3d metals with the B vitamins, their isomers and derivatives (synthesis, structure,

properties, application): Diss..... Doc. of chemical sciences. – Tashkent, 1991. – p.333.

52. Yunuskhodjayev A.N. Coordination compounds of 3d metals with B group vitamins and their some derivatives: Diss..... Phd. of chemical sciences. – Tashkent, 1983. –p. 34.

Publications and conference papers

53. Shodiyev Q.Q. The development of pharmaceutical industry in Uzbekistan// Pharmaceutical journal. – Tashkent, 2004. - №1. - p. 5-7.

54. Pyatigorskaya N.V., Nogayeva A.T. On unity of securing the quality system and technological documents on manufacturing the drug facilities // Conference paper of XI international congress “Health and education in XXI century. Scientific and fundamental aspects of concepts of health and healthy way of life”.– M., 2010.–p.157.

55. Yunuskhodjayev A.N. Pharmaceutical sector of Uzbekistan. Status and prospects // Pharmaceutical journal. –Tashkent, 2011. - №1. - p.3-6.

56. Yunuskhodjayev A.N., Zaynutdinova X.S. The development of regulations on pharmaceutical activity: issues and their solutions // Pharmaceutical journal. –Tashkent, - 2011. - №4. - p. 17-22.

Internet resources

57. http://pharma.net.ua/analytic/analysis/12853-mirovoj_farmaceuticheskij-rynok-v-2014-godu-gonka-prodolzhaetsja

58. <http://www.piluli.kharkov.ua/drugs/drug/1606/>

59. <http://www.piluli.kharkov.ua/drugs/drug/maltofer/>

60. <http://www.piluli.kharkov.ua/drugs/drug/sorbifer-durules/>

61. <http://www.webapteka.ru/drugbase/name3444.html>

62. [http://apteka.uz/remedy_group_sp_ooo_firma_proizvoditel/piracinm-\(puracinm-rg\)_qullash_buyicha_yuriqnoma](http://apteka.uz/remedy_group_sp_ooo_firma_proizvoditel/piracinm-(puracinm-rg)_qullash_buyicha_yuriqnoma)

63. <http://blog.nielsen.com/nielsenwire/consumer/global-healthcare-calls-for-target-marketing/>

4. <http://top.uz/good/%7B4E5A57AB-EAA9-459D-9FE6-D94D77C7559%7D.html>

APPENDIX

APPENDIX

Package type	Shelf life, year	Description	Average mass and to exception from it, %	Strength to break, to grateness, N	Disintegration, min	Dissolution, %	Quantity, %
Bottle from colorless glass	Initial sample	Light green colored, specific odored, cylindrical tablets	0,518±3,6	97,89	4,20	93,15	99,78
Bottle from dark glass	--	--	0,514±2,8	98,05	3,48	95,44	99,63
Uncelled strip pack	--	--	0,508±1,6	99,56	3,65	96,80	98,93
Celled strip pack	--	--	0,487±2,6	99,12	4,36	94,67	98,89



Электронный научный журнал Современные проблемы науки и образования

ISSN 2070-7428

"Перечень" ВАК

ИФ РИНЦ = 0,941

 ЛИЧНЫЙ ПОРТФЕЛЬ ([HTTP://LK.SCIENCE-EDUCATION.RU](http://lk.science-education.ru))

Главная (/ru) / Выпуски журнала (/ru/issue) / Выпуск журнала №2 за 2016 год

Информация о выпуске

Разделы

Медицинские науки (14.01.00, 14.02.00, 14.03.00)

Педагогические науки (13.00.00)

Биологические науки (03.02.00)

Выпуск журнала №2 за 2016 год

Медицинские науки (14 01 00, 14 02 00, 14 03 00)

ПРИМЕНЕНИЕ АЛМАЗОПОДОБНЫХ ПОКРЫТИЙ ПРИ ЭНДОПРОТЕЗИРОВАНИИ КРУПНЫХ
СОСТАВОВ: ОТ ТЕОРИИ К ВОЗМОЖНОЙ ПРАКТИКЕ (/ru/article/view?id=24130)

Бердюгин К. А., Шлыков И. Л., Макарова Э. Б., Рубштейн А. П., Владимиров А. Б., Бердюгина О. В.

ОСОБЕННОСТИ ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ЗДОРОВЬЯ НАСЕЛЕНИЯ, ПРОЖИВАЮЩЕГО В
ЗОНЕ ЭКОЛОГИЧЕСКОГО НЕБЛАГОПОЛУЧИЯ (/ru/article/view?id=24144)

Садетова А. Ж., Шокабаева А. С., Алшынбекова Г. К., Машина Т. Ф., Дорошилова А. В., Калиева И.
Саттыбаев К. Е.

БИОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ЦИТОАРХИТЕКТОНИЧЕСКИХ СВОЙСТВ И АГРЕГАЦИИ
ЛИМФОЦИТОВ У ЗДОРОВЫХ ЛЮДЕЙ, РЕГУЛЯРНО ИСПЫТЫВАЮЩИХ В ХОДЕ ТРУДОВОЙ
ДЕЯТЕЛЬНОСТИ ЗНАЧИТЕЛЬНЫЕ ФИЗИЧЕСКИЕ И ЭМОЦИОНАЛЬНЫЕ НАГРУЗКИ (/ru/article/view?

Министерство сельского хозяйства Российской Федерации
Новосибирский государственный аграрный университет

МАТЕРИАЛЫ XIV МЕЖДУНАРОДНОЙ
НАУЧНО-ПРАКТИЧЕСКОЙ
СТУДЕНЧЕСКОЙ КОНФЕРЕНЦИИ
«ХИМИЯ И ЖИЗНЬ»

Новосибирск 2015

Химия и жизнь: сб. статей междунар. науч.-практ. конф. / Новосибир. аграр. ун-т. – Новосибирск, 2015. – 352 с.

ISBN 978-5-94477-160-5

Научный редактор: д-р биол. наук, профессор *Т.И. Бокова*
Рецензент сборника: канд. биол. наук, доцент *Ю.И. Коваль*

В сборник включены доклады выступлений участников XIV международной научно-практической студенческой конференции «Химия и жизнь», проводимой на базе кафедры химии Новосибирского государственного аграрного университета. В сборник вошли материалы по следующим направлениям: строение, свойства биологически активных веществ и их использование в сельском хозяйстве; химия пищи; экологическая химия и биотехнологии; макро- и микроэлементы, их соединения и участие в биологических процессах; медицинские аспекты химических процессов; аналитическая химия.

Материалы сборника предназначены для студентов, аспирантов и преподавателей.

Конференция организована ФГБОУ ВПО НГАУ.

Оргкомитет выражает признательность всем авторам и их научным руководителям, принявшим участие в организации сборника материалов конференции. Приглашаем Вас к дальнейшему сотрудничеству. Будем благодарны за высказанные замечания и пожелания к последующим изданиям сборника: chemi_ngau@mail.ru.

Авторы опубликованных статей несут ответственность за научную чистоту, достоверность и точность приведенных фактов, цифр, статистических данных, собственных имен и прочих сведений, а также за разглашение данных, не подлежащих открытой публикации. Комментарии приводятся в авторской редакции.

ISBN 978-5-94477-160-5

Химия и жизнь: сб. статей междунар. науч.-практ. конф. / Ново-
аграр. ун-т.– Новосибирск, 2015. – 352 с.

ISBN 978-5-94477-160-5

Научный редактор: д-р биол. наук, профессор *Т.И. Бокова*
Рецензент сборника: канд. биол. наук, доцент *Ю.И. Коваль*

В сборник включены доклады выступлений участников XIV меж-
ной научно-практической студенческой конференции «Химия и
жизнь», проводимой на базе кафедры химии Новосибирского государ-
ственного аграрного университета. В сборник вошли материалы по сле-
дующим направлениям: строение, свойства биологически активных ве-
ществ и их использование в сельском хозяйстве; химия пищи; экологи-
ческая химия и биотехнологии; макро- и микроэлементы, их соединения и
роль в биологических процессах; медицинские аспекты химических про-
цессов; аналитическая химия.

Материалы сборника предназначены для студентов, аспирантов и
преподавателей.

Конференция организована ФГБОУ ВПО НГАУ.

Редакционный комитет выражает признательность всем авторам и их научным
руководителям, принявшим участие в организации сборника материалов
конференции. Приглашаем Вас к дальнейшему сотрудничеству. Будем
благодарны за высказанные замечания и пожелания к последующим из-
даниям сборника: chemi_ngau@mail.ru.

*Авторы опубликованных статей несут ответственность за на-
дежность, чистоту, достоверность и точность приведенных фактов,
цифровых и статистических данных, собственных имен и прочих сведений, а
также за разглашение данных, не подлежащих открытой публикации.
Вопросы приводятся в авторской редакции.*

978-5-94477-160-5

© ФГБОУ ВПО НГАУ, 2015

СИНТЕЗ И ИЗУЧЕНИЕ СМЕШАННОЛИГАНДНЫХ КООРДИНАЦИОННЫХ СОЕДИНЕНИЙ АЦЕТАТОВ БИОМЕТАЛЛОВ С ПИРИДОКСИНОМ И АМИДОМ НИКОТИНОВОЙ КИСЛОТЫ

М.Х. Шамшиддинова

Научные руководители:

канд. хим. наук, и.о доц. А.К. Сайдалиева,

д-р хим. наук, проф. А.А. Шабилалов

Ташкентский фармацевтический институт

В работе приведены методы синтеза и результаты анализа смешаннолигандных комплексных соединений кобальта(II), никеля(II), цинка с витамином B₆ и амидом никотиновой кислоты. Спектроскопическими методами выявлено строение координационных соединений.

Цель. В организме химические элементы находятся преимущественно в виде координационных соединений, которые, как правило, обладают большой биологической активностью, терапевтической эффективностью и безопасностью [1]. Расширение класса смешаннолигандных комплексов изучаемых витаминов с биометаллами, имеет как теоретическое, так и прикладное значение.

Материалы и методика синтеза. При выполнении настоящего исследования применялись ацетаты Co(II), Ni(II), Zn марки «ч.д.а.» и «х.ч.». Лиганды – амид никотиновой кислоты (АЗ-ПМК), пиридоксин (ПН) солянокислый марки «фармакопейный».

Синтез комплексов. [Co(ПН)(АЗ-ПМК)(ПН-Н)CH₃COO]×5H₂O. К раствору 0,006 моля ПН и столько же АЗ-ПМК в 35 мл этанола добавили суспензию 0,002 моля Co(CH₃COO)₂×4H₂O в 5 мл этанола. Смесь перемешивали на магнитной мешалка 3 часа. Затем осадок отделили, промыли этанолом и эфиром. [Ni(ПН)(АЗ-ПМК)(ПН-Н)CH₃COO]×H₂O. 0,006 моль ПН и 0,006 моля АЗ-ПМК растворили в 35

мл этанола. К раствору лигандов добавили 0,002 моля сухой соли $\text{Ni}(\text{CH}_3\text{COO})_2 \times 4\text{H}_2\text{O}$ и перемешивали на магнитной мешалке 2 часа. Затем маточный раствор отделили фильтрованием, выпарили до 1/3 части первоначального объема. Комплекс осадили и промыли эфиром.

$[\text{Zn}(\text{A3-ПМК})(\text{ПН-Н})\text{CH}_3\text{COO}(\text{OH}_2)_2] \times 4\text{H}_2\text{O}$. 0,006 моль ПН растворили в 30 мл этанола. К нему прибавили 0,002 моль сухого А3-ПМК. К раствору лигандов по каплям добавили 0,002 моля $\text{Zn}(\text{CH}_3\text{COO})_2 \times 2\text{H}_2\text{O}$ в 6 мл этанола. После перемешивания вещество высадили и промыли эфиром. Соединения идентифицированы рентгенофазовым и элементным анализами.

Результаты. Для изучения строения сняты ИК-спектры, ЭСДО (электронный спектр диффузного отражения) и изучены термические свойства соединений.

В ИК-спектре комплекса $[\text{Zn}(\text{A3-ПМК})(\text{ПН-Н})\text{CH}_3\text{COO}(\text{OH}_2)_2] \times 4\text{H}_2\text{O}$ наблюдается полоса при 1308 см^{-1} , характерная для фенолятов, а $\nu(\text{C-O})$ спиртовой группы расщеплена и его низкочастотный компонент проявляется около 1016 см^{-1} . В спектре отсутствует интенсивная полоса при 1525 см^{-1} , характерная для соединений, содержащих протонированный гетероатом азота. Очевидно, в соединениях металл замещает водород фенольного гидроксила ПН и образует координационную связь с атомом кислорода спиртового гидроксила. При этом в координации гетероатом азота, вероятно, не участвует. Об этом свидетельствует частота полос кольца около 955 см^{-1} , которая практически одинакова с таковой спектра калиевой соли ПН [2]. Ацетат-ион в соединении является внутрисферным, и, вероятно, проявляет монодентатность. Это подтверждается разницей между $\nu_{\text{as}}(\text{COO})$ и $\nu_{\text{s}}(\text{COO})$ равной 168 см^{-1} , которое практически одинаково с таковыми для комплекса $[\text{Zn}(\text{ПН})_2(\text{CH}_3\text{COO})_2] \times 6\text{H}_2\text{O}$, где ацетат ион монодентатен [3]. По данным дериватографического анализа координационный полиэдр металла достраивается до октаэдра за счет координации двух из имеющихся в соединении молекул воды. Полосы спектра при 570 и 415 см^{-1}

¹, отнесенные к $\nu(\text{Zn-N})$ $\nu(\text{Zn-O})$ соответственно, подтверждают N, 5O координацию. Судя по составу, а также по ИК-спектрам комплексов $[\text{Co}(\text{ПН})(\text{АЗ-ПМК})(\text{ПН-Н})\text{CH}_3\text{COO}]\times 5\text{H}_2\text{O}$ и $[\text{Ni}(\text{ПН})(\text{АЗ-ПМК})(\text{ПН-Н})\text{CH}_3\text{COO}]\times \text{H}_2\text{O}$ ПН в них координирован двояко, т.е. с протонированием и без протонирования гетероатома азота. В соединениях, вероятно, реализуется октаэдрическая структура с монодентатной координацией молекулы АЗ-ПМК и ацетат-иона. С последним хорошо согласуется значение разницы между $\nu_{\text{as}}(\text{COO})$ и $\nu_{\text{s}}(\text{COO})$ в спектре комплексов, равной $\sim 140 \text{ см}^{-1}$. Значение $\Delta\nu$ практически одинаково с таковыми для формамидных комплексов Ni(II) и Co(II) состава $\text{ML}_4(\text{CH}_3\text{COO})_2$ в которых ацетат-ион координирован монодентатно. Октаэдрическое окружение металла комплексообразователя в этих соединениях подтверждено изучением их ЭСДО.

Выводы. Установлено, что пиридоксину с монодентатным N-лигандом характерна хелатная координация к металлу атомами кислорода фенольной и 4-оксиметильной групп в цвиттер-ионной форме с миграцией водорода фенольного гидроксила к азоту гетероцикла или депротонированной форме.

Библиографический список

1. Кудрин А.В., Громова О.А. Микроэлементы в неврологии. – М.: ГЭОТАР – Наука, 2006. – С.11–85.
2. Юнусходжаев А.Н. Координационные соединения 3d-металлов с витаминами группы В и их некоторыми производными: дис.... канд. хим. наук. – Ташкент, 1983. – С. 34, 79, 111.
3. Шабилалов А.А. Координационная химия биосоединений 3d-металлов с некоторыми витаминами группы В, их изомерами и производными (синтез, строение, свойства, применение): дис.... д-ра хим. наук. – Ташкент, 1991. – С. 333.



МИРЗО УЛУГБЕК НОМИДАГИ
ЎЗБЕКИСТОН МИЛЛИЙ УНИВЕРСИТЕТИ

SHAMSHIDDINOVA MAFTUNA XUSNIDIN QIZI

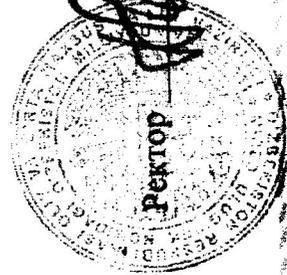
2015 йил 25-26 май кунлари Ёш олим ва талабаларнинг

«XXI АСР – ИНТЕЛЛЕКТУАЛ

АВЛОД АСРИ»

Тошкент шаҳри ва Тошкент вилояти ҳудудий
илмий-амалий конференциясида

“Synthesis and study of the mixed liganded coordination compound of nickel chloride with
pyridoxine and the amide of nicotinic acid”
мавзусида маъруза билан қатнашди.



Ҳамедов



ЎЗБЕКИСТОН РЕСПУБЛИКАСИ ФАНААР АКАДЕМИЯСИ
АКАДЕМИК О.С. СОДИКОВ НОМИДАГИ
БИООРГАНИК КИМЁ ИНСТИТУТИ



ТАЪЛИМ, ФАҲН ВА МАДАНИЯТ
МАСАЛАЛАРИ БЎЙИЧА
БИРЛАШГАН МИЛЛАТЛАР ТАШКИЛОТИ

СЕРТИФИКАТ

CERTIFICATE

This is to certify that:

Maftuna Shamsiddinova



*“Талаба ва ёш тадқиқотчилар учун кристаллография бўйича
малака ошириш машғулотлари” амалий курсини муваффақиятли тамомлади*
*has successfully completed "Training courses for capacity building of students and
young scientists in the field of crystallography"*



A.S. Turayev
Институт директори проф. Тураев А.С.
Director of the Institute prof. A.S. Turayev

Илмий марказ бошлиғи проф. Ибрагимов Б. Т.
Head of research center prof. B. T. Ibragimov

ТОШКЕНТ - 2015



**МИРЗО УЛУҒБЕК НОМИДАГИ
ЎЗБЕКИСТОН МИЛЛИЙ УНИВЕРСИТЕТИ**

SHAMSHIDDINOVA MAFTUNA XUSNIDIN QIZI

2015 йил 25-26 май кунлари Ёш олим ва талабаларнинг

**«XXI АСР – ИНТЕЛЛЕКТУАЛ
АВЛОД АСРИ»**

Тошкент шаҳри ва Тошкент вилояти ҳудудий
илмий-амалий конференциясида

**“Synthesis and study of the mixed liganded coordination compound of nickel chloride with
pyridoxine and the amide of nicotinic acid”
мавзусида маъруза билан қатнашди.**


Ректор **Мухамедов**



СЕРТИФИКАТ

Тошкент фармацевтика институти магистранти

ШАМШИДДИНОВА МАФТУНАХОН ХУСНИДИН ҚИЗИ

ёш олимлар ва талабаларнинг "XXI аср – интеллектуал авлод асри" шиори остида ўтказилган ҳудудий анжуманда галиб бўлиб, шу анжуманинг республика босқичида фаол иштирок этганлиги учун тақдирланди

(Тошкент, 2015 йил 19-20 ноябрь)



Ўзбекистон Республикаси Президентининг
"Истеъдод" жамғармаси ижрочи директори

A. Paradashev

А. Пардашев



Тошкент давлат иқтисодиёт
фармация университети ректори

M. Boltaboev

М. Болтабаев

№ 138



SERTIFIKAT

Shamshiddinova Noftunaxon Dusmudin qizi

"ERTANGI KUN BIZNIKI, MARRA BIZNIKI!"

shiori ostida 2015-yil 16-21 noyabr kunlari
Toshkent shahrida o'tkazilgan
"Yoshlar haftaligi" ishtirokchisi



Tashkiliy qo'mita raisi
Q. Quronboyev



MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY

CERTIFICATE OF ATTENDANCE

This is to certify that
Shamshiddinova M. Kh.

attended the

**XXIII International Scientific and Practical Conference of young scientists and students
«TOPICAL ISSUES OF NEW DRUGS DEVELOPMENT»**

National University of Pharmacy
Ukraine, Kharkiv, April 21, 2016

**Rector, Doctor of Pharmacy,
Doctor of Chemistry,
Academician of the National
Academy of Science, Professor**

V. P. Chernykh





O'zbekiston Respublikasi
Prezidentining "Istiqod" jamg'armasi

O'zbekiston Respublikasi
Fanlar Akademiyasi

O'zbekiston Respublikasi
Oliy va o'rta maxsus ta'lim vazirligi

Fan va texnologiyalarni rivojlantirishni
muvofiqlashtirish qo'mitasi

O'zbekiston
"Kamolot" yoshlar ijtimoiy harakati

Toshkent davlat
iqtisodiyot universiteti



Yosh olimlar va talabalarning "XXI asr - Intellektual avlod asri" shiori
ostidagi hududiy (Toshkent shahri va Toshkent viloyati uchun) ilmiy-amaliy konferensiyasida
"Tabiiy fanlar" yo'nalishi bo'yicha faol ishtirok etib, faxrli I o'rinni egallagani uchun

Shamshiddinova Maftuna Xusnidin qizi

I darajali

DIPLOM



bilan taqdirlanadi

Toshkent davlat iqtisodiyot
universiteti rektori

B. Loqub

B. Xodiyev

No 12